IQWiG Reports – Commission No. A22-70

Pembrolizumab (cervical cancer) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Pembrolizumab (Zervixkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2022). Please note: This document was translated by an external translator and 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
AEOSI	adverse event of special interest
AUC	area under the curve
BSA	body surface area
CPS	combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life – 5 Dimensions
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
PFS	progression-free survival
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-CX24	Quality of Life Questionnaire Cervical Cancer Module
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
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 pembrolizumab (in combination with chemotherapy with or without bevacizumab). 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 26 July 2022.

Research question

The aim of the present report is to assess the added benefit of pembrolizumab in combination with chemotherapy with or without bevacizumab (hereinafter referred to as "pembrolizumab + chemotherapy ± bevacizumab") in comparison with the appropriate comparator therapy (ACT) in the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express programmed cell death ligand 1 (PD-L1) (with a combined positive score [CPS] ≥ 1).

The research questions shown in Table 2 were derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pembrolizumab + chemotherapy ± bevacizumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); first line[d]	Therapy of physician's choice[c]
2	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); patients after first-line chemotherapy and for whom further antineoplastic therapy is an option	Therapy of physician's choice[e]

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that surgery and/or (chemo)radiotherapy with curative intent is not (or no longer) an option at the time the therapeutic decision is taken, and that treatment is palliative. Hence, the non-drug treatment options of surgery and (chemo)radiotherapy do not constitute ACT options. This does not affect the use of resection and/or radiotherapy as palliative individualized treatment options for symptom control depending on the location and symptoms of metastases.
c. Guidelines recommend the drugs cisplatin, carboplatin, paclitaxel, and bevacizumab. The drug paclitaxel has not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication versus those used in practice and/or recommended by the guidelines. As part of therapy of physician's choice, the following treatment options are deemed suitable comparators: cisplatin in combination with paclitaxel ± bevacizumab; carboplatin in combination with paclitaxel ± bevacizumab (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); cisplatin in combination with topotecan; carboplatin in combination with topotecan (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); paclitaxel in combination with topotecan ± bevacizumab (only for patients for whom platinum-containing chemotherapy is not an option).
d. No prior systemic chemotherapy except when used as a radiosensitizer.
e. For the present patient population, guidelines list various treatment options. Several of the drugs recommended by guidelines are not approved in the present therapeutic indication: nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, and pembrolizumab. In the present therapeutic indication, the marketing authorizations of the drugs ifosfamide and topotecan are each linked to the combination partner of cisplatin. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended by guidelines and/or used in practice. In the context of therapy of physician's choice, the following monotherapies are deemed suitable comparators: nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan, pembrolizumab (for patients with PD-L1-positive metastatic cervical cancer).

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- research question 1: patients with persistent, recurrent, or metastatic cervical cancer; first line
- research question 2: patients with persistent, recurrent, or metastatic cervical cancer; patients after first-line chemotherapy for whom further antineoplastic therapy is an option

For both research questions, the company concurred with the 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) were used for the derivation of added benefit.

Research question 1: patients with persistent, recurrent, or metastatic cervical cancer; first line

Study pool and study design

The KEYNOTE 826 study was included for the benefit assessment of pembrolizumab + chemotherapy ± bevacizumab.

The KEYNOTE 826 study is an ongoing, double-blind RCT comparing pembrolizumab + chemotherapy ± bevacizumab versus placebo + chemotherapy ± bevacizumab. In both study arms, chemotherapy comprised the drug combinations of cisplatin + paclitaxel or carboplatin + paclitaxel.

The KEYNOTE 826 study included adult patients with persistent, recurrent, or metastatic cervical cancer (squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma) which was not previously treated with systemic chemotherapy. Furthermore, patients had to be non-amenable to curative therapy such as surgery and/or radiation and were to be in good general health in accordance with Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) ≤ 1. Patients were enrolled in the study irrespective of PD-L1 expression.

A total of 617 patients were enrolled in the KEYNOTE 826 study and randomized at a 1:1 ratio to treatment with either pembrolizumab + chemotherapy ± bevacizumab (N = 308) or placebo + chemotherapy ± bevacizumab (N = 309).

In the KEYNOTE 826 study, pembrolizumab was administered in 3-week cycles, largely in line with the specifications of the Summary of Product Characteristics (SPC).

The KEYNOTE 826 study specified for all chemotherapy components and for bevacizumab to be administered in accordance with the local marketing authorization and/or practice. Overall, the dosage of all drug components used in the KEYNOTE 826 study seems plausible.

A minimum of 35.9% of the KEYNOTE 826 study's relevant subpopulation (maximum 38.5%; discrepant information provided in Module 4 A) received no combination therapy with bevacizumab. According to the S3 guideline, patients with metastatic or recurrent/persistent cervical cancer should simultaneously receive bevacizumab. The reasons why additional bevacizumab treatment was deemed not medically indicated by the investigator were surveyed in the sample case report form, but they are not provided in the study documents. Furthermore, the criteria based on which the investigators arrived at their treatment decision were not provided. It therefore remains unclear whether all patients who did not receive combination therapy with bevacizumab treatment were in fact not medically indicated for bevacizumab. This uncertainty was taken into account in the assessment of the certainty of the KEYNOTE 826 study results.

Primary outcomes of the KEYNOTE 826 study were overall survival and progression-free survival (PFS). Secondary outcomes were from the categories: morbidity, health-related quality of life, and side effects.

Relevant subpopulation of the KEYNOTE 826 study

According to the marketing authorization, pembrolizumab in combination with chemotherapy with or without bevacizumab is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 (CPS ≥ 1).

In accordance with the marketing authorization for pembrolizumab, the company's Module 4 A discusses exclusively the subpopulation of KEYNOTE 826 study participants with PD-L1 CPS ≥ 1. This subpopulation comprises 273 patients in the intervention arm and 275 patients in the comparator arm.

Overall, the subpopulation analysed by the company adequately reflects the relevant population in the present therapeutic indication and is therefore used in the present benefit assessment.

Implementation of the appropriate comparator therapy in the KEYNOTE 826 study

Implementation of the combination chemotherapy in the KEYNOTE 826 study's relevant subpopulation

Pembrolizumab in combination with chemotherapy with or without bevacizumab is approved for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 (CPS ≥ 1). In the KEYNOTE 826 study, chemotherapy comprised the drug combinations of paclitaxel + cisplatin or paclitaxel + carboplatin.

According to the S3 guideline, the combination of paclitaxel + cisplatin and bevacizumab is the standard in the first-line therapy of persistent, recurrent, or metastatic cervical cancer. In patients with prior cisplatin treatment, carboplatin represents an equivalent substitute for cisplatin.

In the KEYNOTE 826 study, 15.2% of the relevant subpopulation received a combination chemotherapy consisting of cisplatin + paclitaxel, while 81.2% of the relevant subpopulation received a combination chemotherapy consisting of carboplatin + paclitaxel. For 3.5% of the relevant subpopulation, information on the chemotherapy drug combination is missing.

Among the KEYNOTE 826 participants who received carboplatin + paclitaxel combination chemotherapy, 57.8% had been previously treated with cisplatin (chemo)radiotherapy, while 42.2% were cisplatin-naive. For 54.8% of the cisplatin-naive patients (18.8% of the relevant subpopulation), a medical rationale was provided for excluding cisplatin treatment. In 45.2% of cisplatin-naive patients (15.5% of the relevant subpopulation), no medical rationale precluded the use of cisplatin.

Overall, at least 15.5% of the KEYNOTE 826 study's relevant subpopulation received carboplatin instead of cisplatin combination chemotherapy contrary to the recommendations of the S3 guideline. The uncertainty resulting from this deviation is taken into account in the assessment of the certainty of results from the KEYNOTE 826 study.

KEYNOTE 826 study allows drawing conclusions on added benefit only for a subpopulation

The comparator therapies used in the KEYNOTE 826 study represent relevant treatment options in the present therapeutic indication. However, the employed comparator therapies do not include all options for therapy of physician's choice which are available in the therapeutic indication (as per the G-BA's note on the ACT). Consequently, the KEYNOTE 826 study lends itself to drawing conclusions on the added benefit of pembrolizumab + chemotherapy ± bevacizumab only in patients for whom cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab represents a suitable therapy of physician's choice. No data are available for patients who are indicated for other options for therapy of physician's choice.

Data cut-off

The KEYNOTE 826 study is still ongoing. At the time of the benefit assessment, the 1st data cut-off from 3 May 2021 was available. The results of the 1st data cut-off were used for the benefit assessment.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 826 study. The outcome-specific risk of bias for the results of all patient-relevant outcomes except overall survival and discontinuation due to adverse events (AEs) was rated as high. Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is reduced.

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under risk of bias, the certainty of conclusions of the study results is reduced due to deviations from guideline recommendations regarding the use of bevacizumab and cisplatin. Based on the KEYNOTE 826 study, at most hints, e.g. of an added benefit, can therefore be derived.

Results

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

Morbidity

Symptoms (surveyed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 [EORTC QLQ-C30])

- *Dyspnoea*

For the outcome of dyspnoea, a statistically significant difference was found to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This difference was no more than marginal, however. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab; an added benefit is therefore not proven.

- *Fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhoea*

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, or diarrhoea. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

Symptoms (surveyed with the EORTC QLQ – Cervical Cancer Module [CX24])

- *Peripheral neuropathy*

For the outcome of peripheral neuropathy, a statistically significant difference was found to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This difference was no more than marginal, however. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab; an added benefit is therefore not proven.

- *Symptom experience, lymphoedema, menopausal symptoms, sexual/vaginal functioning*

No statistically significant difference between treatment groups was found for any of the outcomes of symptom experience, lymphoedema, or menopausal symptoms. No usable data are available for the outcome of sexual/vaginal functioning. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

- *Health status (surveyed using the European Quality of Life – 5 Dimensions [EQ-5D] visual analogue scale [VAS])*

For the outcome of health status, a statistically significant difference was found in favour of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This difference was no more than marginal, however. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ C30

- *Global health status*

No statistically significant difference between treatment arms was shown for the outcome of global health status, but there was an effect modification by the characteristic of age. For patients aged < 65 years, this results in a hint of added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab. In patients aged ≥ 65 years, this results in a hint of lesser benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for this outcome.

- *Physical functioning, role functioning, emotional functioning, social functioning*

No statistically significant difference between treatment groups was shown for any of the outcomes of physical functioning, role functioning, emotional functioning, cognitive functioning, or social functioning. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

EORTC Quality of Life Questionnaire – Cervical Cancer Module (QLQ-CX24)

- *Sexual activity, dyspareunia worries, sexual activity and sexual experience, sexual enjoyment, body image*

No statistically significant difference between treatment groups was found for any of the outcomes of sexual activity, dyspareunia worries, sexual activity and sexual experience, or body image. No usable data are available for the outcome of sexual enjoyment. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs) and severe AEs

No statistically significant difference between treatment groups was shown for the outcomes of SAEs or severe AEs. This results in no hint of greater or lesser harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for either of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab compared with placebo + chemotherapy ± bevacizumab was shown for the outcome of discontinuation due to AEs (at least 1 drug component). This results in a hint of greater harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

Specific AEs

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

For each of the outcomes of immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference was found to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of greater harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for each of them.

- *Skin and subcutaneous tissue disorders (severe AEs)*

For the outcome of skin and subcutaneous tissue disorders (severe AEs), there was a statistically significant difference to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of greater harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

Research question 2: patients with persistent, recurrent, or metastatic cervical cancer; patients after first-line chemotherapy for whom further antineoplastic therapy is an option

Results

No data are available for assessing the added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with the ACT in patients with persistent, recurrent, or metastatic cervical cancer and PD-L1-expressing tumours (CPS ≥ 1) for whom further antineoplastic therapy is an option after first-line chemotherapy. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab 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]

On the basis of the presented results, the probability and extent of added benefit of the drug pembrolizumab (in combination with chemotherapy with or without bevacizumab) in comparison with the ACT is assessed as follows:

All things considered, for research question 1, there are both favourable and unfavourable effects of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. In terms of favourable effects, there is a hint of major added

[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].

benefit for the outcome of overall survival. Additionally, there is an effect modification by the subgroup characteristic of age. For the outcome of global health status, there is a hint of minor added benefit in patients < 65 years as well as a hint of lesser benefit in patients aged ≥ 65 years. In terms of unfavourable effects, there are furthermore hints of greater harm, some of major extent, for each of the outcomes of immune-mediated SAEs, immune-mediated severe AEs, skin and subcutaneous tissue disorders (severe AEs), and discontinuation due to AEs. In this context, it is safe to assume that the outcomes of skin and subcutaneous tissue disorders (severe AEs) and immune-mediated severe AEs exhibit substantial overlap. Overall, the unfavourable effects do not call into question the major added benefit in the outcome of overall survival.

In summary, there is a hint of major added benefit for patients with persistent, recurrent, or metastatic cervical cancer and PD-L1-expressing tumours (CPS ≥ 1) without prior systemic chemotherapy (except when used as a radiosensitizer) for whom the ACT of cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab is a suitable therapy of physician's choice.

There is no proof of added benefit of pembrolizumab + chemotherapy ± bevacizumab in patients for whom cisplatin + paclitaxel ± bevacizumab is not a suitable treatment option.

For research question 2, the company has submitted no data for assessing the added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with the ACT in patients with persistent, recurrent, or metastatic cervical cancer and PD-L1-expressing tumours (CPS ≥ 1) for whom further antineoplastic therapy is an option after first-line chemotherapy. For these patients, there is therefore no proof of added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with the ACT.

Table 3 presents a summary of the probability and extent of added benefit of pembrolizumab (in combination with chemotherapy with or without bevacizumab).

Table 3: Pembrolizumab + chemotherapy ± bevacizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); first line[e]	Therapy of physician's choice[c]	▪ Patients for whom cisplatin or carboplatin + paclitaxel ± bevacizumab is a suitable therapy of physician's choice: hint of major added benefit[d] ▪ Patients for whom cisplatin or carboplatin + paclitaxel ± bevacizumab is no suitable therapy of physician's choice: added benefit not proven
2	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); patients after first-line chemotherapy and for whom further antineoplastic therapy is an option	Therapy of physician's choice[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that surgery and/or (chemo)radiotherapy with curative intent is not (or no longer) an option at the time the therapeutic decision is taken, and that treatment is palliative. Hence, the non-drug treatment options of surgery and (chemo)radiotherapy do not constitute ACT options. This does not affect the use of resection and/or radiotherapy as palliative individualized treatment options for symptom control depending on the location and symptoms of metastases.
c. Guidelines recommend the drugs cisplatin, carboplatin, paclitaxel, and bevacizumab. The drug paclitaxel has not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication versus those used in practice and/or recommended by the guidelines. As part of therapy of physician's choice, the following treatment options are deemed suitable comparators: cisplatin in combination with paclitaxel ± bevacizumab; carboplatin in combination with paclitaxel ± bevacizumab (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); cisplatin in combination with topotecan; carboplatin in combination with topotecan (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); paclitaxel in combination with topotecan ± bevacizumab (only for patients for whom platinum-containing chemotherapy is not an option).
d. The KEYNOTE 826 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.
e. No prior systemic chemotherapy except when used as a radiosensitizer.
f. For the present patient population, guidelines list various treatment options. Several of the drugs recommended by guidelines are not approved in the present therapeutic indication: nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, and pembrolizumab. In the present therapeutic indication, the marketing authorizations of the drugs ifosfamide and topotecan are each linked to the combination partner of cisplatin. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended by guidelines and/or used in practice. In the context of therapy of physician's choice, the following monotherapies are deemed suitable comparators: nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan, pembrolizumab (for patients with PD-L1-positive metastatic cervical cancer).

ACT: appropriate comparator therapy; CPS: combined positive score; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

The approach for deriving an overall conclusion on the added benefit constitutes a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of pembrolizumab in combination with chemotherapy with or without bevacizumab (hereinafter referred to as "pembrolizumab + chemotherapy ± bevacizumab") in comparison with the ACT for treating adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 with a CPS ≥ 1.

The research questions shown in Table 4 were derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab + chemotherapy ± bevacizumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); first line[d]	Therapy of physician's choice[c]
2	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); patients after first-line chemotherapy and for whom further antineoplastic therapy is an option	Therapy of physician's choice[e]

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that surgery and/or (chemo)radiotherapy with curative intent is not (or no longer) an option at the time the therapeutic decision is taken, and that treatment is palliative. Hence, the non-drug treatment options of surgery and (chemo)radiotherapy do not constitute ACT options. This does not affect the use of resection and/or radiotherapy as palliative individualized treatment options for symptom control depending on the location and symptoms of metastases.
c. Guidelines recommend the drugs cisplatin, carboplatin, paclitaxel, and bevacizumab. The drug paclitaxel has not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication versus those used in practice and/or recommended by the guidelines. As part of therapy of physician's choice, the following treatment options are deemed suitable comparators: cisplatin in combination with paclitaxel ± bevacizumab; carboplatin in combination with paclitaxel ± bevacizumab (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); cisplatin in combination with topotecan; carboplatin in combination with topotecan (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); paclitaxel in combination with topotecan ± bevacizumab (only for patients for whom platinum-containing chemotherapy is not an option).
d. No prior systemic chemotherapy except when used as a radiosensitizer.
e. For the present patient population, guidelines list various treatment options. Several of the drugs recommended by guidelines are not approved in the present therapeutic indication: nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, and pembrolizumab. In the present therapeutic indication, the marketing authorizations of the drugs ifosfamide and topotecan are each linked to the combination partner of cisplatin. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended by guidelines and/or used in practice. In the context of therapy of physician's choice, the following monotherapies are deemed suitable comparators: nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan, pembrolizumab (for patients with PD-L1-positive metastatic cervical cancer).

ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

In the present benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- research question 1: patients with persistent, recurrent, or metastatic cervical cancer; first line
- research question 2 : patients with persistent, recurrent, or metastatic cervical cancer; patients after first-line chemotherapy for whom further antineoplastic therapy is an option

For both research questions, the company concurred with the 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 were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: patients with persistent, recurrent, or metastatic cervical cancer; first line

I 3.1 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 pembrolizumab (status: 4 May 2022)
- bibliographical literature search on pembrolizumab (last search on 4 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 4 May 2022)
- search on the G-BA website for pembrolizumab (last search on 4 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 11 August 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

I 3.1.1 Studies included

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

Table 5: Study pool of the company – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication and other sources[d] (yes/no [citation])
KEYNOTE 826	Yes	Yes	No	Yes [2]	Yes [3-5]	Yes [6,7]

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Study for which the company was sponsor.
c. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
d. Other sources: documents from the search on the G-BA website and other publicly available sources.
CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The KEYNOTE 826 study was included for the benefit assessment of pembrolizumab + chemotherapy ± bevacizumab. This concurs with the company's study pool.

The KEYNOTE 826 study compared pembrolizumab + chemotherapy ± bevacizumab versus the treatment options of cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab. Therefore, this study lends itself to drawing conclusions on the added benefit of pembrolizumab + chemotherapy ± bevacizumab only for the patient group for whom cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab is a suitable therapy of physician's choice. No data are available for patients for whom other treatment options of physician's choice (see Table 4) are suitable.

Section I 3.1.2 describes the subpopulation relevant for the present benefit assessment, patients with tumours expressing PD-L1 (CPS ≥ 1%).

I 3.1.2 Study characteristics

Table 6 and Table 7 present the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE 826	RCT, double-blind, parallel-group	Adult patients with persistent, recurrent, or metastatic cervical cancer[c] ▪ without prior systemic chemotherapy[d] ▪ without curative treatment options (e.g. surgery and/or radiation) ▪ ECOG-PS 0 or 1	Pembrolizumab + chemotherapy[a] ± bevacizumab[e] (N = 308) Placebo + chemotherapy[a] ± bevacizumab[e] (N = 309) Relevant subpopulation thereof (PD-L1 CPS ≥ 1): Pembrolizumab + chemotherapy[a] ± bevacizumab[e] (n = 273) Placebo + chemotherapy[a] ± bevacizumab[e] (n = 275)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, occurrence of intercurrent disease, or a maximum of 35 treatment cycles[f] with pembrolizumab or 6 treatment cycles[g] with chemotherapy, or treatment discontinuation upon the physician's or patient's discretion Observation[h]: outcome-specific, at the longest until death, withdrawal of consent, or study end	151 study centres in Argentina, Australia, Canada, Chile, Columbia, France, Germany, Israel, Italy, Japan, Mexico, Peru, Russia, South Korea, Spain, Taiwan, Turkey, Ukraine, United States 10/2018 – ongoing Data cut-off: 3 May 2021[i]	Primary: overall survival, PFS Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the included study – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (multipage table)

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

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include information only on outcomes which are relevant and available for this benefit assessment.
c. Squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix.
d. Prior chemotherapy used as a radiosensitizer was allowed, provided it had been completed ≥ 2 weeks prior to randomization and all treatment-related toxicities had subsided.
e. Bevacizumab treatment was administered as per local practice and at the investigator's discretion. The decision whether bevacizumab was to be a component of the study medication had to be taken prior to randomization.
f. Patients who achieved complete response according to RECIST 1.1 after at least 8 pembrolizumab treatment cycles were allowed to interrupt treatment after 2 further cycles. In the event of subsequent confirmed disease progression (second-course phase), treatment continuation for a further 17 cycles was allowed. In the event of subsequent confirmed disease progression, patients who exhibited tumour response after 35 pembrolizumab cycles (stable disease or partial/complete response) and did not receive any other follow-up therapy were likewise allowed a further 17 cycles of pembrolizumab treatment. At the time of the 1st data cut-off (3 May 2021), no patients were in the second-course phase.
g. In consultation with the company, patients who tolerated chemotherapy and exhibited persistent clinical benefit were allowed to continue chemotherapy beyond 6 cycles.
h. Outcome-specific information is provided in Table 8.
i. Predefined interim analysis after about 370 PFS events in the relevant subpopulation (PD-L1, CPS ≥ 1).

AE: adverse event; CPS: combined positive score; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized (enrolled) patients; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (multipage table)

Study	Intervention[b]	Comparison[b]
KEYNOTE 826	Pembrolizumab 200 mg i.v. in the form of a 30-minute infusion, every 3 weeks + Paclitaxel 175 mg/m² BSA i.v., every 3 weeks + Cisplatin[c] 50 mg/m² BSA i.v., every 3 weeks[d] or Carboplatin AUC 5 i.v., every 3 weeks ± Bevacizumab[e] 15 mg/kg i.v., every 3 weeks	Placebo i.v. in the form of a 30-minute infusion, every 3 weeks + Paclitaxel 175 mg/m² BSA i.v., every 3 weeks + Cisplatin[c] 50 mg/m² BSA i.v., every 3 weeks[d] or Carboplatin AUC 5 i.v., every 3 weeks ± Bevacizumab[e] 15 mg/kg i.v., every 3 weeks
	Dose adjustments[f]: ▪ Pembrolizumab: dose interruption (for a maximum of 12 weeks) / treatment discontinuation due to toxicity (e.g. immune-mediated AEs, infusion-related reactions) allowed ▪ Paclitaxel, cisplatin, carboplatin, bevacizumab: dose reduction, dose interruption (for a maximum of 6 weeks) or treatment discontinuation allowed in accordance with local approval and/or local practice	
	Non-permitted pretreatment: ▪ Systemic chemotherapy against cervical cancer[g] ▪ Radiotherapy[h] ≤ 2 weeks before randomization ▪ Antibodies against PD-1, PD-L1, PD-L2, or drugs against another stimulating or co-inhibitory T-cell receptor (e.g. CTLA-4, OX 40, CD137) or any other immunotherapy ▪ Chronic systemic steroid therapy (> 10 mg prednisone equivalent / day) or another form of immunosuppressant therapy ≤ 7 days prior to randomization **Non-permitted concomitant treatment:** ▪ Other antineoplastic systemic chemotherapy or biologic treatment ▪ Other chemotherapies ▪ Immunotherapies ▪ Radiotherapy[i] **Permitted concomitant treatment** ▪ Corticosteroids ▫ for the treatment of immune-mediated AEs ▫ for the prevention of allergic reactions to therapy[j] or as a premedication prior to chemotherapy ▫ in physiological dosage of 10 mg/day prednisone or equivalent ▫ inhaled for asthma treatment ▪ G-CSF for the prophylactic treatment of treatment-related neutropenia	

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (multipage table)

Study	Intervention[b]	Comparison[b]
a. Paclitaxel + cisplatin or paclitaxel + carboplatin. b. Prior to randomization, the investigator defined whether the patient was to be treated with cisplatin or carboplatin and whether the patient was to receive bevacizumab. The following is the recommended sequence for study treatment: 1) pembrolizumab or placebo; 2) paclitaxel; 3) cisplatin or carboplatin; 4) bevacizumab. c. Where clinically necessary (e.g. due to impaired kidney function), patients were allowed to switch from cisplatin to carboplatin during the study. d. Cisplatin administration was allowed on both Day 1 and Day 2 of each 3-week cycle, provided this was in line with local practice. e. After discontinuation of all other study medications, the locally applicable marketing authorization and local practice allowed continuing bevacizumab treatment until disease progression or the occurrence of unacceptable toxicity. f. Where the investigator clearly determined the specific component causing toxicity, it was possible to interrupt, reduce (except pembrolizumab), or discontinue any drug of the combination therapy independently from the other drugs. g. Prior chemotherapy used as a radiosensitizer was allowed, provided it had been completed ≥ 2 weeks prior to randomization and all treatment-related toxicities had subsided. h. In palliative radiotherapy (≤ 2 weeks) of non-CNS diseases, a 1-week wash-out phase was allowed. i. In consultation with the company, palliative radiotherapy of symptomatic lesions was allowed, provided it did not affect any target lesion in accordance with RECIST 1.1. j. E.g. to paclitaxel and/or i.v. contrast agents. AE: adverse event; AUC: area under the curve; BSA: body surface area; CD137: Cluster of Differentiation 137; CNS: central nervous system; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; G-CSF: granulocyte colony-stimulating factor; i.v.: intravenous; OX-40: cluster of differentiation 134; PD-1: programmed cell death 1; PD-L1/2: programmed cell death ligand 1/2; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours		

The KEYNOTE 826 study is an ongoing, double-blind RCT comparing pembrolizumab + chemotherapy ± bevacizumab versus placebo + chemotherapy ± bevacizumab. In both study arms, chemotherapy comprised the drug combinations of cisplatin + paclitaxel or carboplatin + paclitaxel. The choice of combination chemotherapy and the decision on including or excluding bevacizumab in treatment was made by the investigator before randomization.

The KEYNOTE 826 study included adult patients with persistent, recurrent, or metastatic cervical cancer (squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma) which was not previously treated with systemic chemotherapy. Furthermore, patients had to be nonamenable to curative therapy such as surgery and/or radiation and were to be in good general health in accordance with Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) ≤ 1.

A prerequisite for randomization was the availability of an archived tumour tissue sample or a newly obtained core or excisional biopsy of a tumour lesion not previously irradiated for the prospective determination of the PD-L1 status. This determination was performed by a central laboratory using the PD-L1 ICH 22C3 pharmDx assay [6] . Patients were enrolled in the study irrespective of PD-L1 expression.

A total of 617 patients were enrolled in the KEYNOTE 826 study and randomized at a 1:1 ratio to treatment with either pembrolizumab + chemotherapy ± bevacizumab (N = 308) or placebo + chemotherapy ± bevacizumab (N = 309). Stratification was based on the characteristics of metastatic spread (in accordance with the International Federation of Gynecology and Obstetrics [FIGO] 2009, stage IVB) at the time of the diagnosis (yes versus no), investigator's decision on using bevacizumab (yes versus no), and PD-L1 status (CPS < 1 versus 1 ≤ CPS < 10 versus CPS ≥ 10).

In the KEYNOTE 826 study, pembrolizumab treatment was administered in 3-week cycles, largely in line with SPC specifications [8]. However, study treatment with pembrolizumab was restricted to a maximum of 35 treatment cycles (approximately 2 years). According to the marketing authorization, pembrolizumab treatment is to be continued until cancer progression or the occurrence of unacceptable toxicity. At the 1st data cut-off (3 May 2021), a total of 20 patients in the intervention arm and 9 patients in the comparator arm had been treated for ≥ 24 months; therefore, the difference in defined treatment duration between the SPC and study protocol is negligible.

The KEYNOTE 826 study specified for all chemotherapy components and for bevacizumab to be administered in accordance with the local marketing authorization and/or practice.

In both study arms, chemotherapy involved paclitaxel in combination with cisplatin or carboplatin. In the present therapeutic indication, paclitaxel is not approved [9], but according to the S3 guideline on the diagnosis, therapy, and follow-up of patients with cervical cancer, this drug in combination with cisplatin and bevacizumab is deemed standard in the first-line therapy of persistent, recurrent, or metastatic cervical cancer [10]. In the KEYNOTE 826 study, the paclitaxel dose was 175 mg/m^2 body surface area (BSA). In accordance with the S3 guideline, the recommended paclitaxel dose in combination with cisplatin is 135 mg/m^2 BSA [10]. In the KEYNOTE 826 study, 15.2% of the relevant subpopulation received combination chemotherapy with paclitaxel and cisplatin. Most patients in the KEYNOTE 826 study received carboplatin chemotherapy (81.2% of the relevant subpopulation). The JCOG 0505 study [10], for instance, likewise dosed paclitaxel, in combination with carboplatin, at 175 mg/m^2 BSA. This is in line with the dosage administered in the KEYNOTE 826 study.

Both cisplatin and carboplatin are approved in the present therapeutic indication [11,12]. In the KEYNOTE 826 study, paclitaxel combination chemotherapy comprised 50 mg/m^2 BSA of either cisplatin or carboplatin, in line with an area under the curve (AUC) of 5, administered every 3 weeks. Cisplatin dosage in the KEYNOTE 826 study is in line with the recommendations of the S3 guideline [10]. The SPC does not provide the carboplatin dosage in AUC for this drug combination [12]. The S3 guideline likewise does not address the carboplatin dosage [10]. In Module 3 A, the company notes that the SPC specifies no defined paclitaxel and carboplatin dosages for patients with cervical cancer and that the dosages chosen in the KEYNOTE 826 study represent those commonly used in clinical trials on patients with cervical

cancer [13-15]. Overall, the company's argument is persuasive, and the paclitaxel and carboplatin dosages seem plausible.

The KEYNOTE 826 study further limited paclitaxel plus cisplatin or carboplatin therapy to 6 treatment cycles. This limitation is not found in the cisplatin and carboplatin SPCs [11,12]. However, patients who tolerated the combination chemotherapy and exhibited clinical benefit were allowed to continue therapy with paclitaxel as well as cisplatin or carboplatin beyond 6 treatment cycles after obtaining the company's consent; therefore, this limitation is of no further consequence for the present benefit assessment.

The KEYNOTE 826 study administered the 15 mg/kg bevacizumab dose in accordance with approval [16]. However, at least 35.9% (maximum 38.5%; discrepant information provided in Module 4 A) of the relevant subpopulation received no combination therapy with bevacizumab. According to the S3 guideline, patients with metastatic or recurrent/persistent cervical cancer should simultaneously receive bevacizumab [10]. The reasons why additional bevacizumab treatment was deemed not medically indicated by the investigator were surveyed in the sample case report form, but they are not provided in the study documents. Furthermore, the criteria based on which the investigators arrived at their treatment decision were not provided. It therefore remains unclear whether all patients who did not receive combination therapy with bevacizumab treatment were in fact not medically indicated for bevacizumab. This uncertainty was taken into account in the assessment of the certainty of the KEYNOTE 826 study results.

The study population was treated either until disease progression, until the occurrence of unacceptable toxicity or of intercurrent disease, or until patients had received a maximum of 35 treatment cycles with pembrolizumab or 6 chemotherapy treatment cycles (paclitaxel, cisplatin, or carboplatin). Furthermore, patients who achieved complete response as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria 1.1 after at least 8 pembrolizumab cycles were allowed to interrupt treatment after 2 further cycles. Subsequently, treatment continuation for a further 17 cycles was allowed in the event of confirmed disease progression (second-course phase). Additionally, patients who exhibited tumour response (stable disease or partial/complete response) after 35 pembrolizumab cycles and did not receive any other follow-up therapy were also eligible for a further 17 cycles of pembrolizumab in the event of subsequent confirmed disease progression. At the time of the 1st data cut-off (3 May 2021), no patients were in the second-course phase.

Primary outcomes of the KEYNOTE 826 study were overall survival and PFS. Secondary outcomes were from the morbidity, health-related quality of life, and side effects categories.

Relevant subpopulation of the KEYNOTE 826 study

According to the marketing authorization, pembrolizumab, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 (CPS ≥ 1).

The KEYNOTE 826 study included patients irrespective of their PD-L1 expression status. Before randomization, only an archival tumour tissue sample or newly obtained core or excisional biopsy of a tumour lesion not previously irradiated had to be available for all patients for the prospective determination of PD-L1 status.

In accordance with the marketing authorization for pembrolizumab, the company's Module 4 A discusses exclusively the subpopulation of KEYNOTE 826 study participants with PD-L1 CPS ≥ 1. This subpopulation comprises 273 patients in the intervention arm and 275 patients in the comparator arm.

Overall, the subpopulation analysed by the company adequately reflects the relevant population in the present therapeutic indication and is therefore used in the present benefit assessment.

Implementation of the appropriate comparator therapy in the KEYNOTE 826 study

Implementation of the combination chemotherapy in the relevant subpopulation of the KEYNOTE 826 study

Pembrolizumab, in combination with chemotherapy with or without bevacizumab, is approved for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 (CPS ≥ 1). In the KEYNOTE 826 study, chemotherapy comprised the drug combinations of paclitaxel + cisplatin or paclitaxel + carboplatin.

According to the S3 guideline, the combination of paclitaxel + cisplatin and bevacizumab is the standard in the first-line therapy of persistent, recurrent, or metastatic cervical cancer [10]. It further specifies that, in patients with prior cisplatin treatment, carboplatin is an equivalent substitute for cisplatin [10]. In its notes on the ACT, the G-BA likewise points out that the combination of carboplatin + paclitaxel ± bevacizumab is indicated only for patients with prior cisplatin treatment for whom cisplatin is not a suitable therapy [17].

In the KEYNOTE 826 study, 15.2% of the relevant subpopulation received a combination chemotherapy consisting of cisplatin + paclitaxel, while 81.2% of the relevant subpopulation received a combination chemotherapy consisting of carboplatin + paclitaxel. For 3.5% of the relevant subpopulation, information on the chemotherapy drug combination is missing.

Among the KEYNOTE 826 participants who received carboplatin + paclitaxel combination chemotherapy, 57.8% had been previously treated with cisplatin (chemo)radiotherapy, while 42.2% were cisplatin-naive. For 54.8% of the cisplatin-naive patients (18.8% of the relevant subpopulation), a medical rationale was provided for excluding cisplatin treatment. In 45.2% of cisplatin-naive patients (15.5% of the relevant subpopulation), no medical rationale precluded the use of cisplatin. Technically, combination chemotherapy consisting of cisplatin + paclitaxel would have been medically indicated for these patients because this combination chemotherapy is the standard first-line therapy of persistent, recurrent, or metastatic cervical cancer [10].

Furthermore, according to the S3 guideline, another round of cisplatin therapy is possible after (chemo)radiotherapy with cisplatin as radiosensitizer [10]. It is unclear whether another round of cisplatin therapy was an option for some of the patients with prior cisplatin therapy.

Overall, at least 15.5% of the KEYNOTE 826 study's relevant subpopulation received carboplatin instead of cisplatin combination chemotherapy contrary to the recommendations of the S3 guideline. The uncertainty resulting from this deviation from the guideline recommendations is accounted for in the assessment of the certainty of results from the KEYNOTE 826 study.

KEYNOTE 826 study allows drawing conclusions on added benefit only for a subpopulation

The G-BA specified treatment of physician's choice as the ACT, and its notes list the following combination therapies as treatment options:

- cisplatin in combination with paclitaxel ± bevacizumab
- carboplatin in combination with paclitaxel ± bevacizumab (only for patients with prior cisplatin therapy and patients for whom cisplatin is not an option)
- cisplatin in combination with topotecan
- carboplatin in combination with topotecan (only for patients with prior cisplatin therapy and patients for whom cisplatin is not an option)
- paclitaxel in combination with topotecan ± bevacizumab (only for patients for whom platinum-containing chemotherapy is not an option)

The KEYNOTE 826 study presented by the company used cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab in the comparator arm. No comparison with the other treatment options is available.

According to the S3 guideline, the combination therapies used in the KEYNOTE 826 study (cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab) are the most important treatment options in the present therapeutic indication [10]. The guidelines issued by the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) likewise list cisplatin + paclitaxel ± bevacizumab as the preferred first-line therapy in metastatic or recurrent cervical cancer [18,19].

Overall, the comparator therapies used in the KEYNOTE 826 study represent relevant treatment options in the present therapeutic indication. However, the employed ACTs do not cover all options for therapy of physician's choice which are available in the therapeutic indication. Consequently, the KEYNOTE 826 study lends itself to drawing conclusions on the added benefit of pembrolizumab + chemotherapy ± bevacizumab only in patients for whom cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab represents a

suitable option for therapy of physician's choice. No data are available for patients who are indicated for other options for therapy of physician's choice.

Data cut-off

The KEYNOTE 826 study is still ongoing. At the time of the benefit assessment, the 1st data cut-off from 3 May 2021 was available. This is a predefined interim analysis conducted after 370 PFS events in the relevant subpopulation with CPS ≥ 1.

The results of the 1st data cut-off were used for the benefit assessment.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab

Study Outcome category Outcome	Planned follow-up observation
KEYNOTE 826	
Mortality	
Overall survival	Until death, withdrawal of consent, or study end
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-CX24)	Until 37 days after treatment end[b, c] or until the start of a subsequent cancer therapy
Health status (EQ-5D VAS)	Until 37 days after treatment end[b, c] or until the start of a subsequent cancer therapy
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-CX24)	Until 37 days after treatment end[b, c] or start of a subsequent cancer therapy
Side effects	
AEs/severe AEs[d]	Until 30 days after treatment end
SAEs	Until 90 days after treatment end or until 30 days after treatment end if a new anticancer treatment is initiated

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Corresponds to the visit at the safety follow-up; safety follow-up is not necessary if the EOT visit is ≥ 30 days after the last dose of the study medication.
c. Module 4 A presents the survey time points only until treatment end (maximum until Week 99) (see Section I 3.2.1).
d. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-CX24: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cervical Cancer Module; EOT: end of treatment; EQ-5D: European Quality of Life – 5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes of morbidity, health-related quality of life, and side effects are systematically shortened because they were surveyed only for the period of treatment with the study medication (plus 37 days for morbidity and health-related quality of life outcomes and up to 30 days for AEs or a maximum of 90 days for SAEs). For these outcomes, data are therefore available only for the shortened follow-up period. Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival.

Characteristics of the relevant subpopulation

Table 9 shows the patient characteristics for the relevant subpopulation of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Study Characteristic Category	**Pembrolizumab + chemotherapy[a] ± bevacizumab N[b] = 273**	**Placebo + chemotherapy[a] ± bevacizumab N[b] = 275**
KEYNOTE 826		
Age [years], mean (SD)	51 (12)	51 (13)
Sex [f/m], %	100/0	100/0
Ancestry, n (%)		
Asian	57 (21)	41 (15)
White	153 (56)	172 (63)
Other[c]	63 (23)[d]	62 (23)[d]
Region, n (%)		
WHO Stratum A[e]	123 (45)	115 (42)
Rest of the world	150 (55)	160 (58)
ECOG-PS, n (%)		
0	160 (59)	148 (54)
1	111 (41)	127 (46)
2	1 (< 1)	0 (0)
Missing	1 (< 1)	0 (0)
Disease status at study start[f], n (%)		
Metastatic	56 (21)	59 (22)
Persistent or recurrent with distant metastases at baseline	170 (62)	156 (57)
Persistent or recurrent without distant metastases at baseline	47 (17)	60 (22)
Prior lines of therapy, n (%)		
Chemoradiotherapy and surgery	43 (16)	48 (18)
Radiation and surgery	18 (7)	21 (8)
Chemoradiotherapy only	112 (41)	103 (38)
Radiation only	28 (10)	21 (8)
Surgery only	16 (6)	23 (8)
No documentation of prior therapy within 28 days before baseline	56 (21)	59 (22)
PD-L1 status, n (%)		
1 ≤ CPS < 10	115 (42)	116 (42)
CPS ≥ 10	158 (58)	159 (58)
Use of bevacizumab in the study[g], n (%)		
Yes	175 (64)	171 (62)
No	98 (36)	104 (38)
Treatment discontinuation, n (%)[h]	169 (62)	224 (82)
Study discontinuation, n (%)[i]	120 (44)	157 (57)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Study Characteristic Category	Pembrolizumab + chemotherapy[a] ± bevacizumab N[b] = 273	Placebo + chemotherapy[a] ± bevacizumab N[b] = 275

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Number of randomized patients. Values based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Includes “Native Americans or Alaska Native”, “Black”, “Native American or Alaska Native and Black”, “Native American or Alaska Native and White”, “Native American or Alaska Native and Asian”, “Black and White”, “Not applicable”, and “Missing”.
d. Institute's calculation.
e. Australia, Canada, Germany, France, Italy, Israel, Japan, Spain, and the United States.
f. Metastatic includes patients with involvement of para-aortic lymph nodes.
g. Module 4 A provides discrepant information on the percentage of patients treated with versus without bevacizumab. It indicates that, in the relevant subpopulation, the percentage of patients not receiving bevacizumab was somewhere between 36.9% and 38.5%.
h. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (39% vs. 57%), AEs (11% vs. 8%), and withdrawal of consent (5% vs. 7%).
i. Common reasons for study discontinuation in the intervention arm vs. control arm were death (42% vs. 56%) and withdrawal of consent (2% vs. 1%).

AE: adverse event; CPS: combined positive score; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; f: female; m: male; n: number of patients in the category; N: number of randomized (or enrolled) patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; WHO: World Health Organization

The patient characteristics in the included relevant subpopulation were balanced between the 2 treatment arms. On average, patients were 51 years of age, mostly of White ancestry (56% versus 63%) and in good general health as per an ECOG-PS of 0 (59% versus 54%). At baseline, the majority of patients in the relevant subpopulation had persistent or recurrent disease with distant metastases (62% versus 57%) and had received chemoradiotherapy as the only prior therapy (41% versus 38%). More than half of the relevant subpopulation was allocated to bevacizumab treatment prior to randomization (64% versus 62%).

Information on the course of the study

Table 10 shows patients’ median treatment duration and the mean/median observation durations for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + chemotherapy[a] ± bevacizumab** **N = 273**	**Placebo + chemotherapy[a] ± bevacizumab** **N = 275**
KEYNOTE 826		
Treatment duration [months]		
Median [min; max]	10.3 [ND]	7.6 [ND]
Mean (SD)	ND	ND
Observation duration [months]		
Overall survival [b]		
Median [min; max]	18.3 [0.5; 29.4]	16.3 [0.3; 29.2]
Mean (SD)	17.2 (6.9)	15.0 (7.3)
Morbidity and health-related quality of life		
Health status (EQ-5D VAS)		
Median [min; max]	11.7 [ND]	8.6 [ND]
Mean (SD)	ND	ND
Symptoms and health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	12.5 [ND]	9.1 [ND]
Mean (SD)	ND	ND
Symptoms and health-related quality of life (EORTC QLQ-CX24)		
Median [min; max]	12.7 [ND]	9.1 [ND]
Mean (SD)	ND	ND
Side effects (AEs)		
AEs, severe AEs[c]		
Median [min; max]	11.3 [ND]	8.6 [ND]
Mean (SD)	ND	ND
SAEs		
Median [min; max]	12.9 [ND]	10.5 [ND]
Mean (SD)	ND	ND

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. The observation duration is defined as the time from randomization until death or until the current data cut-off if the patient is still living.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-CX24: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cervical Cancer Module; EQ-5D: European Quality of Life – 5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; VAS: visual analogue scale

In the KEYNOTE 826 study, the median treatment duration of the relevant subpopulation was longer in the intervention arm, at 10.3 months, than in the comparator arm, at 7.6 months. The median observation duration for the outcome of overall survival is 18.3 months in the intervention arm and 16.3 months in the comparator arm. For the morbidity, health-related quality of life, and side effects outcomes, whose observation durations were linked to treatment end (see Table 8), the observation durations were markedly shortened when compared to overall survival. For these outcomes, conclusions can therefore be drawn only for the time on treatment plus up to 37 days for outcomes of the morbidity and health-related quality of life categories and plus up to 30 days for AEs and severe AEs or for a maximum of 90 days for SAEs. In addition, the between-arm differences in median treatment durations also result in differences in the mean observation period for the outcomes.

Information on subsequent therapies

Table 11 shows the subsequent therapies which patients of the relevant subpopulation received after discontinuing the study medication.

Table 11: Information on the first systemic subsequent therapy[a] – RCT, direct comparison: pembrolizumab + chemotherapy[b] ± bevacizumab versus placebo + chemotherapy[b] ± bevacizumab (relevant subpopulation) (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Pembrolizumab + chemotherapy[b] ± bevacizumab **N = 273**	**Placebo + chemotherapy[b] ± bevacizumab** **N = 275**
KEYNOTE 826		
Total (patients with at least 1 subsequent therapy)	61 (22.3)	78 (28.4)
Anthracyclines and related substances	1 (0.4)	0 (0)
Pegylated liposomal doxorubicin hydrochloride	1 (0.4)	0 (0)
Folic acid analogues	0 (0)	1 (0.4)
Pemetrexed	0 (0)	1 (0.4)
Monoclonal antibodies	6 (2.2)	27 (9.8)
Bevacizumab	4 (1.5)	13 (4.7)
Pembrolizumab	1 (0.4)	9 (3.3)
Tisotumab vedotin	0 (0)	2 (0.7)
Atezolizumab	0 (0)	1 (0.4)
Bintrafusp alfa	0 (0)	1 (0.4)
Cemiplimab	0 (0)	1 (0.4)
Dostarlimab	0 (0)	1 (0.4)
Durvalumab	1 (0.4)	0 (0)
Naptumomab estafenatox	1 (0.4)	0 (0)
Obinutuzumab	1 (0.4)	0 (0)
Nitrogen mustard analogues	0 (0)	1 (0.4)
Ifosfamide	0 (0)	1 (0.4)
Other antineoplastic drugs	13 (4.8)	16 (5.8)
Topotecan	5 (1.8)	7 (2.5)
Irinotecan	4 (1.5)	4 (1.5)
Irinotecan hydrochloride	2 (0.7)	3 (1.1)
Topotecan hydrochloride	2 (0.7)	0 (0)
ALKS 4230	0 (0)	1 (0.4)
Niraparib	0 (0)	1 (0.4)
Platinum compounds	32 (11.7)	35 (12.7)
Carboplatin	23 (8.4)	22 (8.0)
Cisplatin	9 (3.3)	11 (4.0)
Nedaplatin	0 (0)	1 (0.4)
Oxaliplatin	0 (0)	1 (0.4)
Propofol	0 (0)	2 (0.7)
Cabozantinib	0 (0)	1 (0.4)
Selumetinib	0 (0)	1 (0.4)

Table 11: Information on the first systemic subsequent therapy[a] – RCT, direct comparison: pembrolizumab + chemotherapy[b] ± bevacizumab versus placebo + chemotherapy[b] ± bevacizumab (relevant subpopulation) (multipage table)

Study	**Patients with subsequent therapy n (%)**	
Drug class **Drug**	**Pembrolizumab + chemotherapy[b] ± bevacizumab** **N = 273**	**Placebo + chemotherapy[b] ± bevacizumab** **N = 275**
Pyrimidine analogues	18 (6.6)	22 (8.0)
Gemcitabine	10 (3.7)	18 (6.5)
Gemcitabine hydrochloride	3 (1.1)	1 (0.4)
Fluorouracil	2 (0.7)	2 (0.7)
Capecitabine	2 (0.7)	1 (0.4)
Tegafur	1 (0.4)	0 (0)
Taxanes	21 (7.7)	17 (6.2)
Paclitaxel	20 (7.3)	16 (5.8)
Docetaxel	1 (0.4)	1 (0.4)
Vinca alkaloids and analogues	3 (1.1)	2 (0.7)
Vinorelbine	3 (1.1)	2 (0.7)

a. Oncological therapies with missing start date or whose start date was before the end of the last study medication were not deemed subsequent therapies.
b. Paclitaxel + cisplatin or paclitaxel + carboplatin.

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

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.

Among the relevant subpopulation, 22.3% of patients in the intervention arm and 28.4% of those in the comparator arm received their first systemic subsequent therapy after discontinuing the study medication. For most patient in both study arms, said therapy comprised a platinum compound (carboplatin [8.4% versus 8%], cisplatin [3.3% versus 4%]) or a taxane (paclitaxel [7.3% versus 5.8%]). Furthermore, patients in both study arms received, among others, topotecan, irinotecan, and gemcitabine. In case of recurrence or metastases following prior cisplatin chemotherapy, the S3 guideline likewise recommends another round of cisplatin therapy in combination with, among others, topotecan, paclitaxel, or gemcitabine, or the administration of carboplatin with paclitaxel [10].

Furthermore, 3.3% of patients in the comparator arm received pembrolizumab as the first systemic subsequent therapy. According to the S3 guideline, checkpoint inhibitors such as pembrolizumab represent another treatment option [10].

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: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
KEYNOTE 826	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.

ACT: appropriate comparator therapy; RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the KEYNOTE 826 study.

Transferability of the study results to the German health care context

In the company's view, the results of the KEYNOTE 826 study are transferable to the to the German health care context. The company bases this assertion on the characteristics of the investigated patient population, the study design, and the approval-compliant use of pembrolizumab in combination with chemotherapy ± bevacizumab.

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

I 3.2 Results on added benefit

I 3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms, surveyed with the EORTC QLQ-C30
  - symptoms, surveyed with the EORTC QLQ-CX24
  - health status, recorded using the EQ-5D VAS

- Health-related quality of life
  - surveyed with the EORTC QLQ-C30
  - surveyed with the EORTC QLQ-CX24
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs (CTCAE grade ≥ 3)
  - 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: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-CX24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-CX24)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b, d]	Immune-mediated SAEs[b, e]	Immune-mediated severe AEs[b, c, e]	Skin and subcutaneous tissue disorders (SOC, severe AEs[b,c])
KEYNOTE 826	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Excluding AEs ascribed to the progression of the underlying disease, defined as the MedDRA terms of neoplasm progression, malignant neoplasm progression, and disease progression.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Discontinuation of at least 1 drug component.
e. In each case, the operationalization of a specific, predefined PT list presented by the company ("AEOSI") was used; version 20.

AE: adverse event; AEOSI: adverse events of special interest (immune-mediated adverse events); CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Cervical Cancer Module; EQ-5D: European Quality of Life – 5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Notes on the included outcomes and analyses

Morbidity and health-related quality of life

In Module 4 A, the company presents responder analyses for the symptoms and health-related quality of life outcomes (surveyed with the EORTC-QLQ-C30 and the disease-specific module of EORTC QLQ-CX24) as well as the outcome of health status (surveyed using the EQ-5D VAS). In Module 4 A, they are operationalized as time to 1st clinically relevant deterioration (from study start to a subsequent survey of patient-relevant outcomes) by ≥ 15 points each (respective scale range of 0 to 100). This response criterion corresponds to 15% of the respective instrument's scale range. Consequently, these responder analyses are used in the present benefit assessment [1]. The information on the median observation duration for these outcomes shows that the observation duration for these outcomes is shortened relative to overall survival (see Table 10). Consequently, the available responder analyses allow drawing conclusions only on the shortened observation period.

According to information provided in the study protocol, the survey of patient-reported outcomes was terminated 37 days after treatment end or at the start of a subsequent therapy (see Table 8). Module 4 A provides no information on the duration of follow-up observation for these outcomes. The return rates for all questionnaires are available only for treatment duration (up to Week 99). In the present scenario, it remains unclear whether the available responder analyses account for surveys performed for follow-up observation. In principle, the entire observation period, including all follow-up observations, must be included in the analysis.

Furthermore, for the outcomes of sexual/vaginal functioning and sexual enjoyment (each surveyed using the EORTC QLQ-CX24), no usable data are available because baseline values are missing for > 50% of the relevant subpopulation. Module 4 A does not address the reasons for the high percentage of missing values.

Side effects

Immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3)

For the outcomes of immune-mediated SAEs and immune-mediated severe AEs (defined in Module 4 A as adverse events of special interest [AEOSIs]), the continuously updated, predefined list of Preferred Terms (PT), which was presented by the company, is deemed a suitable operationalization and is used in the present benefit assessment. For the relevant subpopulation, however, the company's Module 4 A presents neither analyses for immune-mediated AEs nor subgroup analyses for the outcomes of immune-mediated AEs, immune-mediated SAEs, or immune-mediated severe AEs.

I 3.2.2 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: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a]± bevacizumab

Study	Study level	Outcomes									
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-CX24)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-CX24)	SAEs[b]	Severe AEs[b, c]	Discontinuation due to AEs[b, d]	Immune-mediated SAEs[b, e]	Immune-mediated severe AEs[b,c,e]	Skin and subcutaneous tissue disorders (SOC, severe AEs[b,c])
KEYNOTE 826	L	L	H[f, g]	H[f, g]	H[f, g]	H[f]	H[f]	L[h]	H[f]	H[f]	H[f]

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Excluding AEs ascribed to the progression of the underlying disease, defined as the MedDRA terms of neoplasm progression, malignant neoplasm progression, and disease progression.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Discontinuation of at least 1 drug component.
e. In each case, the operationalization of a specific, predefined PT list presented by the company ("AEOSI") was used; version 20.
f. Incomplete observations for potentially informative reasons with different median observation durations.
g. Decreasing questionnaire response rate over the course of the study.
h. Despite a low risk of bias, the certainty of results was assumed to be limited for the outcome of discontinuation due to AEs (see section below).

AE: adverse event; AEOSI: adverse events of special interest (immune-mediated adverse events); CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life – 5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias was rated as high for the results of all patient-relevant outcomes, except overall survival and discontinuation due to AEs.

The risk of bias for the outcomes of symptoms, health status, and health-related quality of life was rated as high. These outcomes suffer from incomplete observations for potentially informative reasons (largely due to the end of observation occurring at the latest 37 days after discontinuation of treatment, which in turn was predominantly due to disease progression) as well as decreasing questionnaire return rates over the course of the study.

For the outcomes of SAEs, severe AEs, immune-mediated SAEs, immune-mediated severe AEs, and the specific AE of skin and subcutaneous tissue disorders (severe AEs), the risk of

bias of results is likewise rated as high due to incomplete observation for potentially informative reasons.

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

Summary assessment of the certainty of conclusions

Irrespective of the aspects described under risk of bias, the certainty of conclusions of study results is reduced due to the deviations from guideline recommendations regarding the use of bevacizumab and cisplatin as described in Section I 3.1.2. Based on the KEYNOTE 826 study, at most hints, e.g. of an added benefit, can therefore be derived.

I 3.2.3 Results

Table 15 summarizes the results on the comparison of pembrolizumab + chemotherapy ± bevacizumab versus placebo + chemotherapy ± bevacizumab in patients with persistent, recurrent, or metastatic cervical cancer with PD-L1-expressing tumours (CPS ≥ 1). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Kaplan-Meier curves on the presented time-to-event analyses can be found in I Appendix B of the full dossier assessment. Results on common AEs, SAEs, severe AEs, and discontinuations due to AEs are presented in I Appendix C of the full dossier assessment. I Appendix D of the full dossier assessment presents as supplementary information a list of the categories of immune-mediated AEs, immune-mediated SAEs, and immune-mediated severe AEs (information is available only for the total population of the KEYNOTE 826 study) in which events occurred.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + chemotherapy[a] ± bevacizumab**		**Placebo + chemotherapy[a] ± bevacizumab**		**Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab**
	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[b]**
KEYNOTE 826					
Mortality					
Overall survival	273	NR [19.8; NC] 118 (43.2)	275	16.3 [14.5; 19.4] 154 (56.0)	0.64 [0.50; 0.81]; < 0.001
Morbidity					
Symptoms (EORTC QLQ-C30)[c]					
Fatigue	246	3.7 [2.8; 4.6] 159 (64.6)	253	3.6 [2.9; 4.9] 151 (59.7)	1.06 [0.85; 1.33]; 0.613
Nausea and vomiting	246	2.9 [2.4; 3.7] 170 (69.1)	253	2.7 [2.1; 3.9] 171 (67.6)	0.99 [0.80; 1.22]; 0.912
Pain	246	4.5 [3.4; 5.8] 155 (63.0)	253	3.4 [2.3; 4.7] 164 (64.8)	0.94 [0.76; 1.18]; 0.607
Dyspnoea	246	3.6 [2.8; 4.6] 164 (66.7)	253	6.2 [3.6; 8.3] 140 (55.3)	1.30 [1.03; 1.63]; 0.025
Insomnia	246	5.5 [3.7; 7.6] 141 (57.3)	253	6.3 [4.9; 8.7] 137 (54.2)	1.08 [0.85; 1.36]; 0.544
Appetite loss	246	5.5 [4.2; 8.3] 144 (58.5)	253	5.9 [4.5; 7.6] 139 (54.9)	0.99 [0.78; 1.25]; 0.925
Constipation	246	4.1 [2.2; 6.9] 142 (57.7)	253	4.7 [3.0; 7.0] 148 (58.5)	0.99 [0.78; 1.25]; 0.924
Diarrhoea	246	4.2 [2.9; 7.0] 146 (59.3)	253	6.5 [4.9; 9.9] 131 (51.8)	1.21 [0.95; 1.54]; 0.116
Symptoms (EORTC QLQ-CX24)[c]					
Symptom experience	244	NR 70 (28.7)	251	NR 63 (25.1)	1.04 [0.74; 1.46]; 0.831
Lymphoedema	244	9.7 [6.3; 17.4] 123 (50.4)	251	11.1 [6.2; NC] 112 (44.6)	1.06 [0.82; 1.37]; 0.654
Peripheral neuropathy	244	1.4 [1.0; 1.6] 207 (84.8)	251	1.7 [1.4; 2.1] 197 (78.5)	1.22 [1.00; 1.49]; 0.049
Menopausal symptoms	244	5.5 [3.0; 9.1] 134 (54.9)	251	6.9 [5.0; 12.1] 126 (50.2)	1.14 [0.89; 1.46]; 0.285
Sexual/vaginal functioning[d]	No usable data[e]				
Health status (EQ-5D VAS)[f]	248	14.7 [8.0; NC] 116 (46.8)	254	7.3 [5.0; 13.1] 133 (52.4)	0.76 [0.59; 0.98]; 0.034

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + chemotherapy[a] ± bevacizumab**		**Placebo + chemotherapy[a] ± bevacizumab**		**Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab**
	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[b]**
Health-related quality of life					
EORTC QLQ-C30[f]					
Global health status	246	4.1 [3.1; 6.3] 156 (63.4)	253	3.5 [2.8; 4.6] 172 (68.0)	0.85 [0.68; 1.06]; 0.149
Physical functioning	246	6.9 [5.0; 9.3] 135 (54.9)	253	7.0 [5.0; 10.5] 136 (53.8)	0.99 [0.78; 1.26]; 0.942
Role functioning	246	2.1 [1.5; 2.9] 189 (76.8)	253	2.8 [2.1; 3.3] 188 (74.3)	1.00 [0.81; 1.23]; 0.983
Emotional functioning	246	6.9 [5.4; 12.9] 130 (52.8)	253	7.0 [5.7; 13.9] 128 (50.6)	1.02 [0.80; 1.31]; 0.860
Cognitive functioning	246	2.8 [2.1; 3.8] 180 (73.2)	253	3.5 [2.8; 4.4] 166 (65.6)	1.10 [0.89; 1.36]; 0.394
Social functioning	246	2.8 [2.1; 4.1] 173 (70.3)	253	3.5 [2.7; 4.2] 163 (64.4)	1.12 [0.90; 1.39]; 0.322
EORTC QLQ-CX24[f]					
Sexual activity	236	NR 41 (17.4)	248	NR 33 (13.3)	1.16 [0.73; 1.85]; 0.520
Dyspareunia worries, sexual activity, and sexual experience[g]	234	NR 73 (31.2)	244	NR [16.3; NC] 65 (26.6)	1.02 [0.73; 1.43]; 0.918
Sexual enjoyment	No usable data[e]				
Body image	244	5.4 [4.1; 11.8] 131 (53.7)	251	5.6 [3.3; 7.3] 137 (54.6)	0.94 [0.74; 1.19]; 0.591
Side effects					
AEs (supplementary information)[h]	272	0.6 [0.4; 0.6] 270 (99.3)	275	0.4 [0.4; 0.6] 273 (99.3)	–
SAEs[h]	272	68.6 [31.3; NC] 137 (50.4)	275	NR [57.4; NC] 117 (42.5)	1.20 [0.94; 1.54]; 0.148
Severe AEs[h, i]	272	9.1 [7.1; 11.4] 222 (81.6)	275	11.9 [9.1; 13.4] 206 (74.9)	1.19 [0.99; 1.44]; 0.067
Discontinuation due to AEs[h,j]	272	NR [66.1; NC] 106 (39.0)	275	NR 69 (25.1)	1.54 [1.14; 2.09]; 0.005
Immune-mediated AEs (supplementary information)	No data[k]				

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Study Outcome category Outcome	Pembrolizumab + chemotherapy[a] ± bevacizumab		Placebo + chemotherapy[a] ± bevacizumab		Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab
	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[b]
Immune-mediated SAEs[h, l]	272	NR 23 (8.5)	275	NR 10 (3.6)	2.21 [1.05; 4.65]; 0.036
Immune-mediated severe AEs[h, i, l]	272	NR 38 (14.0)	275	NR 14 (5.1)	2.61 [1.41; 4.82]; 0.002
Skin and subcutaneous tissue disorders (SOC, severe AEs[h,i,m])	272	NR 17 (6.3)	275	NR 1 (0.4)	17.46 [2.32; 131.17]; 0.005

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Effect, CI, and p-value: Cox proportional hazards model; for outcomes of the mortality, morbidity, and health-related quality of life categories, stratified by metastasis, PD-L1 status, and investigator's decision regarding bevacizumab use.
c. Time to 1st deterioration. A score increase by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
d. In departure from the company's approach, this scale was assigned to the symptoms category rather than the health-related quality of life category.
e. Over 50% of values missing at baseline.
f. Time to 1st deterioration. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
g. In departure from the company's approach, the scale was assigned to the health-related quality of life category, rather than the symptoms category.
h. Excluding AEs ascribed to progression of the underlying disease, defined as the MedDRA terms of neoplasm progression, malignant neoplasm progression, and disease progression.
i. Operationalized as CTCAE grade ≥ 3.
j. Discontinuation of 1 or more drug components.
k. Data on immune-mediated AEs are available only for the total population (N = 307 vs. N = 309): intervention arm n = 126 (41.0%) vs. comparator arm n = 82 (26.5%).
l. In each case, the operationalization of a specific, predefined PT list presented by the company ("AEOSI") was used; version 20.
m. In the total population (N = 307 vs. N = 309), this includes the following PTs, among others: maculopapular rash (intervention arm n = 6 vs. comparator arm n = 0), rash (n = 3 vs. n = 1), and pruritus (n = 2 vs. n = 0).

AE: adverse event; AEOSI: adverse events of special interest (immune-mediated adverse events); CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Cervical Cancer Module; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PD-L1: programmed cell death ligand 1; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section I 3.2.2).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference was found in favour of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

Morbidity

Symptoms

The symptoms outcomes were surveyed using the EORTC QLQ-C30 and the disease-specific module EORTC QLQ-CX24. Time to 1st deterioration by ≥ 15 points (scale range 0–100) was taken into account.

EORTC QLQ-C30

Dyspnoea

For the outcome of dyspnoea, a statistically significant difference was found to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This difference was no more than marginal, however (see Section I 3.3.1). This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, diarrhoea

No statistically significant difference between treatment groups was shown for any of the outcomes of fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation, or diarrhoea. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

EORTC QLQ-CX24

Peripheral neuropathy

For the outcome of peripheral neuropathy, a statistically significant difference was found to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This difference was no more than marginal, however (see Section I 3.3.1). This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab; an added benefit is therefore not proven.

Symptom experience, lymphoedema, menopausal symptoms, sexual/vaginal functioning

No statistically significant difference between treatment groups was found for any of the outcomes of symptom experience, lymphoedema, or menopausal symptoms. No usable data are available for the outcome of sexual/vaginal functioning. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

Health status

The outcome of health status was surveyed by EQ-5D VAS. Time to 1st deterioration by ≥ 15 points (scale range 0–100) was taken into account.

For the outcome of health status, a statistically significant difference was found in favour of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This difference was no more than marginal, however (see Section I 3.3.1). This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab; an added benefit is therefore not proven.

Health-related quality of life

The health-related quality of life outcomes were surveyed using the EORTC QLQ-C30 and the disease-specific module EORTC QLQ-CX24. Time to 1st deterioration by ≥ 15 points (scale range 0 to 100) was analysed.

EORTC QLQ C30:

Global health status

No statistically significant difference between treatment groups was shown for the outcome of global health status, but there was an effect modification by the characteristic of age (see Section I 3.2.4). For patients aged < 65 years, this results in a hint of added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab. In patients aged ≥ 65 years, this results in a hint of lesser benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for this outcome.

Physical functioning, role functioning, emotional functioning, social functioning

No statistically significant difference between treatment groups was shown for any of the outcomes of physical functioning, role functioning, emotional functioning, cognitive functioning, or social functioning. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

EORTC QLQ-CX24

Sexual activity, dyspareunia worries, sexual activity and sexual experience, sexual enjoyment, body image

No statistically significant difference between treatment groups was found for any of the outcomes of sexual activity, dyspareunia worries, sexual activity and sexual experience, or body image. No usable data are available for the outcome of sexual enjoyment. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for any of them; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

No statistically significant difference between the treatment groups was shown for the outcomes SAEs and severe AEs. This results in no hint of greater or lesser harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for either of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab compared with placebo + chemotherapy ± bevacizumab was shown for the outcome of discontinuation due to AEs (at least 1 drug component). This results in a hint of greater harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

Specific AEs

Immune-mediated SAEs, immune-mediated severe AEs

For each of the outcomes of immune-mediated SAEs and immune-mediated severe AEs, a statistically significant difference was found to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of greater harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab for each of them.

Skin and subcutaneous tissue disorders (severe AEs)

For the outcome of skin and subcutaneous tissue disorders (severe AEs), there was a statistically significant difference to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of greater harm from pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

I 3.2.4 Subgroups and other effect modifiers

The present benefit assessment analysed the subgroup characteristic of age (< 65 years versus ≥ 65 years). This characteristic was predefined for the outcomes of overall survival and PFS.

The company's Module 4 A presents subgroup analyses for all patient-relevant outcomes listed in the dossier, except for the outcomes of immune-mediated SAEs and immune-mediated severe AEs.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only results showing 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 shown 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 (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation)

Study Outcome Characteristic Subgroup	Pembrolizumab + chemotherapy[a] ± bevacizumab		Placebo + chemotherapy[a] ± bevacizumab		Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab	
	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][b]	p-value[b]
KEYNOTE 826						
Health-related quality of life						
EORTC QLQ-C30[c]						
Global health status						
Age						
< 65	208	5.6 [3.7; 8.1] 125 (60.1)	211	3.5 [2.8; 5.1] 143 (67.8)	0.75 [0.59; 0.96]	0.021
≥ 65	38	1.4 [0.8; 2.1] 31 (81.6)	42	3.0 [2.1; 5.6] 29 (69.0)	1.78 [1.07; 2.97]	0.027
Total					Interaction[d]:	0.003

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. HR, CI, and p-value: Cox proportional hazards model.
c. Time to 1st deterioration. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
d. p-value of the likelihood ratio test of interaction between treatment and subgroup.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; RCT: randomized controlled trial

Health-related quality of life

Global health status

For the outcome of global health status (surveyed with the EORTC QLQ-C30), there was an effect modification by the characteristic of age. For patients aged < 65 years, a statistically significant difference was found in favour of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

For patients aged ≥ 65 years, a statistically significant difference was found to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. This results in a hint of lesser benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with chemotherapy ± bevacizumab.

I 3.3 Probability and extent of added benefit

Below, the probability and extent of added benefit is derived on the outcome level for research question 1 (patients with persistent, recurrent, or metastatic cervical cancer; first line), taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

I 3.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 3.2 (see Table 17).

Determination of the outcome category for outcomes on symptoms and 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

Dyspnoea (EORTC QLQ-C30), peripheral neuropathy (EORTC QLQ-CX24)

For the outcomes of dyspnoea and peripheral neuropathy, insufficient severity data are available which would allow classifying them as serious/severe. Both outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Health status (EQ-5D VAS)

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

Side effects

Discontinuation due to AEs

For the outcome of discontinuation due to AEs, insufficient severity data are available which would allow classifying them as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 17: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] ± bevacizumab versus chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Total observation period		
Mortality		
Overall survival	NR vs. 16.3 HR: 0.64 [0.50; 0.81]; p < 0.001 Probability: hint	Outcome category: mortality $CI_u < 0.85$ Added benefit; extent: major
Shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30; 1st deterioration ≥ 15 points)		
Fatigue	3.7 vs. 3.6 HR: 1.06 [0.85; 1.33]; p = 0.613	Lesser/added benefit not proven
Nausea and vomiting	2.9 vs. 2.7 HR: 0.99 [0.80; 1.22] p = 0.912	Lesser/added benefit not proven
Pain	4.5 vs. 3.4 HR: 0.94 [0.76; 1.18]; p = 0.607	Lesser/added benefit not proven
Dyspnoea	3.6 vs. 6.2 HR: 1.30 [1.03; 1.63] HR: 0.77 [0.61; 0.97][d]; p = 0.025	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ lesser/added benefit not proven[e]
Insomnia	5.5 vs. 6.3 HR: 1.08 [0.85; 1.36]; p = 0.544	Lesser/added benefit not proven
Appetite loss	5.5 vs. 5.9 HR: 0.99 [0.78; 1.25]; p = 0.925	Lesser/added benefit not proven
Constipation	4.1 vs. 4.7 HR: 0.99 [0.78; 1.25]; p = 0.924	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] ± bevacizumab versus chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Diarrhoea	4.2 vs. 6.5 HR: 1.21 [0.95; 1.54]; p = 0.116	Lesser/added benefit not proven
Symptoms (EORTC QLQ-CX24; 1st deterioration ≥ 15 points)		
Symptom experience	NR vs. NR HR: 1.04 [0.74; 1.46]; p = 0.831	Lesser/added benefit not proven
Lymphoedema	9.7 vs. 11.1 HR: 1.06 [0.82; 1.37]; p = 0.654	Lesser/added benefit not proven
Peripheral neuropathy	1.4 vs. 1.7 HR: 1.22 [1.00; 1.49] HR: 0.82 [0.67; 1.00][d,f]; p = 0.049	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ lesser/added benefit not proven[e]
Menopausal symptoms	5.5 vs. 6.9 HR: 1.14 [0.89; 1.46]; p = 0.285	Lesser/added benefit not proven
Sexual/vaginal functioning	No usable data	Lesser/added benefit not proven
Health status (EQ-5D VAS)	14.7 vs. 7.3 HR: 0.76 [0.59; 0.98]; p = 0.034	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Health-related quality of life		
EORTC QLQ-C30 (1st deterioration ≥ 15 points)		
Global health status Age		
< 65	5.6 vs. 3.5 HR: 0.75 [0.59; 0.96]; p = 0.021 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit; extent: minor
≥ 65	1.4 vs. 3.0 HR: 1.78 [1.07; 2.97] HR: 0.56 [0.34; 0.93][d]; p = 0.027 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent minor
Physical functioning	6.9 vs. 7.0 HR: 0.99 [0.78; 1.26]; p = 0.942	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] ± bevacizumab versus chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Role functioning	2.1 vs. 2.8 HR: 1.00 [0.81; 1.23]; p = 0.983	Lesser/added benefit not proven
Emotional functioning	6.9 vs. 7.0 HR: 1.02 [0.80; 1.31]; p = 0.860	Lesser/added benefit not proven
Cognitive functioning	2.8 vs. 3.5 HR: 1.10 [0.89; 1.36]; p = 0.394	Lesser/added benefit not proven
Social functioning	2.8 vs. 3.5 HR: 1.12 [0.90; 1.39]; p = 0.322	Lesser/added benefit not proven
EORTC QLQ-CX24 (1st deterioration ≥ 15 points)		
Sexual activity	NR vs. NR HR: 1.16 [0.73; 1.85]; p = 0.520	Lesser/added benefit not proven
Dyspareunia worries, sexual activity and sexual experience	NR vs. NR HR: 1.02 [0.73; 1.43]; p = 0.918	Lesser/added benefit not proven
Sexual enjoyment	No usable data	Lesser/added benefit not proven
Body image	5.4 vs. 5.6 HR: 0.94 [0.74; 1.19]; p = 0.591	Lesser/added benefit not proven
Side effects		
SAEs	68.6 vs. NR HR: 1.20 [0.94; 1.54]; p = 0.148	Greater/lesser harm not proven
Severe AEs	9.1 vs. 11.9 HR: 1.19 [0.99; 1.44]; p = 0.067	Greater/lesser harm not proven
Discontinuation due to AEs	NR vs. NR HR: 1.54 [1.14; 2.09] HR: 0.65 [0.48; 0.88][d]; p = 0.005 Probability: hint	Outcome category: non-serious/non-severe AEs $0.80 \leq CI_u < 0.90$ Greater harm; extent: minor

Table 17: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] ± bevacizumab versus chemotherapy[a] ± bevacizumab (relevant subpopulation) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + chemotherapy[a] ± bevacizumab vs. placebo + chemotherapy[a] ± bevacizumab** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Immune-mediated SAEs	NR vs. NR HR: 2.21 [1.05; 4.65] HR: 0.45 [0.22; 0.95][d]; p = 0.036 Probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: minor
Immune-mediated severe AEs	NR vs. NR HR: 2.61 [1.41; 4.82] HR: 0.38 [0.21; 0.71][d]; p = 0.002 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm; extent: major
Skin and subcutaneous tissue disorders (severe AEs)	NR vs. NR HR: 17.46 [2.32; 131.17] HR: 0.06 [0.01; 0.43][d]; p = 0.005 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Greater harm; extent: major

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size use different limits based on the upper limit of the confidence interval (CI_u).
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Due to the significant p-value, the unrounded CI_u is presumably < 1.00.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-CX24: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cervical Cancer Module; EQ-5D: European Quality of Life – 5 Dimensions; HR: hazard ratio; NR: not reached; SAE: serious adverse event; VAS: visual analogue scale

I 3.3.2 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: Favourable and unfavourable effects from the assessment of pembrolizumab + chemotherapy[a] ± bevacizumab in comparison with chemotherapy[a] ± bevacizumab (relevant subpopulation)

Favourable effects	Unfavourable effects
Total observation period	
Mortality ▪ overall survival: hint of added benefit – extent: major	–
Shortened observation period	
Health-related quality of life ▪ global health status ▫ age (< 65 years): hint of added benefit – extent: minor	Health-related quality of life ▪ global health status ▫ age (≥ 65 years): hint of lesser benefit – extent: minor
–	Serious/severe side effects ▪ immune-mediated SAEs: hint of greater harm – extent: minor ▪ immune-mediated severe AEs: hint of greater harm – extent major ▪ skin and subcutaneous tissue disorders (severe AEs): hint of greater harm – extent: major
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: minor
a. Paclitaxel + cisplatin or paclitaxel + carboplatin. AE: adverse event; SAE: serious adverse event	

Overall, both favourable and unfavourable effects of pembrolizumab + chemotherapy ± bevacizumab were found in comparison with placebo + chemotherapy ± bevacizumab.

In terms of favourable effects, there is a hint of major added benefit for the outcome of overall survival. Additionally, there is an effect modification by the subgroup characteristic of age. For the outcome of global health status, there is a hint of minor added benefit in patients < 65 years as well as a hint of lesser benefit in patients aged ≥ 65 years. In terms of unfavourable effects, there are furthermore hints of greater harm, some of major extent, for each of the outcomes of immune-mediated SAEs, immune-mediated severe AEs, skin and subcutaneous tissue disorders (severe AEs), and discontinuation due to AEs. In this context, it is safe to assume that the outcomes of skin and subcutaneous tissue disorders (severe AEs) and immune-mediated severe AEs exhibit substantial overlap. Overall, the unfavourable effects do not call into question the major added benefit in the outcome of overall survival.

In summary, there is a hint of major added benefit for patients with persistent, recurrent, or metastatic cervical cancer and PD-L1-expressing tumours (CPS ≥ 1) without prior systemic chemotherapy (except when used as a radiosensitizer) for whom the ACT of cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab is a suitable therapy of physician's choice.

There is no proof of added benefit of pembrolizumab + chemotherapy ± bevacizumab in patients for whom cisplatin + paclitaxel ± bevacizumab is not a suitable treatment option.

The assessment described above deviates from the company's assessment, which derived an indication of major added benefit in comparison with all treatment options listed in the G-BA's note on the ACT [17] for the relevant subpopulation with PD-L1-expressing tumours (CPS ≥ 1).

I 4 Research question 2: patients with persistent, recurrent, or metastatic cervical cancer; patients after first-line chemotherapy for whom further antineoplastic therapy is an option

I 4.1 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 pembrolizumab (status: 4 May 2022)
- bibliographical literature search on pembrolizumab (last search on 4 May 2022)
- search in trial registries / trial results databases for studies on pembrolizumab (last search on 4 May 2022)
- search on the G-BA website for pembrolizumab (last search on 4 May 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 11 August 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of completeness of the study pool showed no RCTs directly comparing pembrolizumab + chemotherapy ± bevacizumab versus the ACT in patients with persistent, recurrent, or metastatic cervical cancer and PD-L1-expressing tumours (CPS ≥ 1) after first-line chemotherapy for whom further antineoplastic therapy is an option.

I 4.2 Results on added benefit

No data are available for assessing the added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with the ACT in patients with persistent, recurrent, or metastatic cervical cancer and PD-L1-expressing tumours (CPS ≥ 1) after first-line chemotherapy for whom further antineoplastic therapy is an option. This results in no hint of an added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

The company did not submit any data for assessing the added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with the ACT in patients with persistent, recurrent, or metastatic cervical cancer and PD-L1-expressing tumours (CPS ≥ 1) after first-line chemotherapy for whom further antineoplastic therapy is an option; therefore, there is no proof of added benefit of pembrolizumab + chemotherapy ± bevacizumab in comparison with the ACT for these patients.

This concurs with the company's assessment.

I 5 Probability and extent of added benefit – summary

Table 19 shows a summary of the probability and extent of added benefit of pembrolizumab + chemotherapy ± bevacizumab.

Table 19: Pembrolizumab + chemotherapy ± bevacizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); first line[e]	Therapy of physician's choice[c]	▪ Patients for whom cisplatin or carboplatin + paclitaxel ± bevacizumab is a suitable therapy of physician's choice: hint of major added benefit[d] ▪ Patients for whom cisplatin or carboplatin + paclitaxel ± bevacizumab is no suitable therapy of physician's choice: added benefit not proven
2	Adult patients with persistent, recurrent, or metastatic cervical cancer[b] whose tumours express PD-L1 (CPS ≥ 1); patients after first-line chemotherapy and for whom further antineoplastic therapy is an option	Therapy of physician's choice[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For the present therapeutic indication, the G-BA assumes that surgery and/or (chemo)radiotherapy with curative intent is not (or no longer) an option at the time the therapeutic decision is taken, and that treatment is palliative. Hence, the non-drug treatment options of surgery and (chemo)radiotherapy do not constitute ACT options. This does not affect the use of resection and/or radiotherapy as palliative individualized treatment options for symptom control depending on the location and symptoms of metastases.
c. Guidelines recommend the drugs cisplatin, carboplatin, paclitaxel, and bevacizumab. The drug paclitaxel has not been approved for the present therapeutic indication. There is a discrepancy between the drugs approved in the therapeutic indication versus those used in practice and/or recommended by the guidelines. As part of therapy of physician's choice, the following treatment options are deemed suitable comparators: cisplatin in combination with paclitaxel ± bevacizumab; carboplatin in combination with paclitaxel ± bevacizumab (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); cisplatin in combination with topotecan; carboplatin in combination with topotecan (only for patients with prior cisplatin therapy or patients for whom cisplatin is not an option); paclitaxel in combination with topotecan ± bevacizumab (only for patients for whom platinum-containing chemotherapy is not an option).
d. The KEYNOTE 826 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2.
e. No prior systemic chemotherapy except when used as a radiosensitizer.
f. For the present patient population, guidelines list various treatment options. Several of the drugs recommended by guidelines are not approved in the present therapeutic indication: nab-paclitaxel, vinorelbine, pemetrexed, irinotecan, and pembrolizumab. In the present therapeutic indication, the marketing authorizations of the drugs ifosfamide and topotecan are each linked to the combination partner of cisplatin. There is a discrepancy between the drugs approved in the therapeutic indication and those recommended by guidelines and used in practice. In the context of therapy of physician's choice, the following monotherapies are deemed suitable comparators: nab-paclitaxel, vinorelbine, ifosfamide, topotecan, pemetrexed, irinotecan, pembrolizumab (for patients with PD-L1-positive metastatic cervical cancer).

ACT: appropriate comparator therapy; CPS: combined positive score; ECOG-PS: Eastern Cooperative Oncology Group – Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

The approach for the derivation of an overall conclusion on the added benefit constitutes a proposal by IQWiG. 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.

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