Pembrolizumab (cervical cancer, combination with radiochemotherapy)

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

EXTRACT

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Medical and scientific advice

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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 of persons concerned was received within 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
CI	confidence interval
CPS	Combined positive score
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	external beam radiotherapy
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30
FIGO	International Federation of Gynecology and Obstetrics
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMRT	intensity-modulated radiotherapy
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
PGI-C SD	Patient Global Impression of Change of Sleep Disturbance
PGI-S	Patient Global Impression of Severity
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SPC	Summary of Product Characteristics
VAS	visual analogue scale
VMAT	volumetric modulated arc therapy

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 radiochemotherapy). 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 14 November 2024.

Research question

The aim of the present report is to assess the added benefit of pembrolizumab in combination with radiochemotherapy (external beam radiotherapy [EBRT] followed by brachytherapy) compared with the appropriate comparator therapy (ACT) in patients with locally advanced cervical cancer (stage III to IVA according to the International Federation of Gynecology and Obstetrics [FIGO] 2014) who have not received prior definitive therapy.

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

Table 2: Research question of the benefit assessment of pembrolizumab in combination with radiochemotherapy[a]

Therapeutic indication	**ACT[b]**
Adults with locally advanced cervical cancer (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy	Radiochemotherapy consisting of EBRT in combination with cisplatin (monotherapy), followed by brachytherapy
a. EBRT in combination with cisplatin, followed by brachytherapy. b. Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; EBRT: external beam radiotherapy; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee	

The company deviates from the G-BA's ACT in that it names cisplatin combination chemotherapy as an option as a chemotherapy component of radiochemotherapy in addition to cisplatin monotherapy. This has no consequences for the benefit assessment, as the company presented no data on this additionally named option. The benefit assessment was conducted in comparison with the ACT specified by the G-BA.

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

Study pool and study design

Concurring with the company, the study pool of the present benefit assessment comprises the KEYNOTE A18 study. The KEYNOTE A18 study is an ongoing, double-blind RCT comparing pembrolizumab + radiochemotherapy versus placebo + radiochemotherapy. In each case, radiochemotherapy consisted of external beam radiotherapy in combination with cisplatin, followed by brachytherapy. The study included adult patients with locally advanced high-risk cervical cancer, defined as stage IB2 to IIB (nodal-positive) or stage III to IVA (nodal-positive or nodal-negative) according to FIGO 2014, who had not received prior definitive therapy.

A total of 1060 patients were included and randomly assigned in a 1:1 ratio to either treatment with pembrolizumab + radiochemotherapy (N = 529) or placebo + radiochemotherapy (N = 531).

Only the subpopulation of patients in stage III to IVA according to FIGO 2014 is relevant for the present benefit assessment. These were 296 patients in the intervention arm and 305 patients in the comparator arm. In Module 4 A of the dossier, the company presented results for this subpopulation. These are used for the benefit assessment.

Treatment with pembrolizumab + radiochemotherapy in the intervention arm and placebo + radiochemotherapy in the comparator arm was largely carried out in accordance with the specifications of the Summary of Product Characteristics (SPC) and the recommendations of the current S3 guideline “Diagnosis, Treatment and Follow-up of Patients with Cervical Cancer”.

Primary outcomes of the KEYNOTE A18 study are “progression-free survival (PFS)” and “overall survival”. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

The present benefit assessment used the results from the prespecified 2nd data cut-off of 08 January 2024.

Subsequent therapies

In the KEYNOTE A18 study, around 16% of patients in the intervention arm and around 26% in the comparator arm received at least 1 subsequent systemic antineoplastic therapy. The most frequently administered drugs were paclitaxel, bevacizumab and the platinum compounds cisplatin and carboplatin.

The subsequent therapies used are initially consistent with the recommendations of the S3 guideline “Diagnosis, Treatment and Follow-up of Patients with Cervical Cancer” from 2022, which specifies treatment with cisplatin or carboplatin in combination with paclitaxel and

bevacizumab as a possible therapy for patients with recurrent, persistent or metastatic cervical cancer.

With the approval of pembrolizumab in combination with chemotherapy with or without bevacizumab, another treatment option for the first-line treatment of persistent, recurrent or metastatic cervical cancer with programmed cell death ligand 1 (PD-L1)-expressing tumours (combined positive score [CPS] ≥ 1) was approved in 2022. 'The pivotal study KEYNOTE 826 showed a clear survival benefit of this combination over chemotherapy alone (possibly in combination with bevacizumab). Based on the IQWiG assessment, the G-BA decided that this treatment option has a considerable added benefit. However, pembrolizumab was only used in a few patients in the present KEYNOTE A18 study. Although the tumours expressed PD-L1 in more than 90% of patients, only around 9% (in relation to those patients in the comparator arm who were treated with subsequent systemic therapy) received pembrolizumab. In a more recent international guideline from 2024, pembrolizumab is already recommended as one of the preferred options for patients with persistent, recurrent or metastatic cervical cancer with PD-L1-expressing tumours.

The results of the outcome of overall survival are decisively influenced by the subsequent antineoplastic therapies used after discontinuation of the study treatment. It must be assumed that a relevant proportion of patients would have benefited from the use of the new pembrolizumab combination therapy. This is taken into account in the assessment of the outcome-specific risk of bias and the determination of the extent of the added benefit.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE A18 study.

The outcome-specific risk of bias for the results of the patient-reported outcomes on symptoms, health status and health-related quality of life, recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30), EORTC QLQ - Cervical Cancer Module (CX24) and the EQ-5D visual analogue scale (VAS), is rated as low in each case.

The outcome-specific risk of bias was rated as high for the results on overall survival and on the outcomes of the side effects category except for the outcome of discontinuation due to adverse events (AEs). Although the risk of bias is low for the outcome of discontinuation due to AEs, the certainty of results for this outcome is limited.

Results

Mortality

Overall survival

For the outcome “overall survival”, a statistically significant difference was found in favour of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy. There is a hint of added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

Morbidity

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

No statistically significant difference between the study arms was shown for any of the outcomes “fatigue”, “nausea and vomiting”, “pain”, “dyspnoea”, “insomnia”, “appetite loss” and “constipation”. In each case, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

For the outcome of diarrhoea, a statistically significant difference was found to the disadvantage of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy. The standardized mean difference (SMD) was analysed to examine the relevance of the result. The 95% confidence interval (CI) of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. There is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

EORTC QLQ-CX24 (symptom experience, lymphoedema, peripheral neuropathy, menopausal symptoms and sexual/vaginal functioning)

No statistically significant difference between the study arms was found for any of the outcomes of symptom experience, lymphoedema, peripheral neuropathy or menopausal symptoms. In each case, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

No usable data are available for the outcome of sexual/vaginal functioning. Therefore, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

Health status

EQ-5D VAS

There was no statistically significant difference between study arms for the outcome of EQ-5D VAS. There is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (global health status, physical functioning, role functioning, cognitive functioning, social functioning and emotional functioning)

No statistically significant difference between the study arms was shown for any of the following outcomes: global health status, physical functioning, role functioning, cognitive functioning and social functioning. In each case, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

For the outcome "emotional functioning", a statistically significant difference was found in favour of pembrolizumab + radiochemotherapy versus placebo + radiochemotherapy. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. There is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

EORTC QLQ-CX24 (sexual activity, worries about painful intercourse, sexual enjoyment and body image)

There are no usable data available for each of the outcomes of sexual activity, worries about dyspareunia, sexual enjoyment and body image. Therefore, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy in any case; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, there is no statistically significant difference between the study arms. There is no hint of greater or lesser harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy was shown for the

outcome of severe AEs (CTCAE grade ≥ 3). There is a hint of greater harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

Discontinuation due to AEs

There was no statistically significant difference between the study arms for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Immune-related severe AEs (CTCAE grade ≥ 3), anaemia (SAEs) and hypokalaemia (severe AEs)

A statistically significant difference to the disadvantage of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy was shown for each of the outcomes “immune-related severe AEs” (CTCAE grade ≥ 3)”, “anaemia” (SAEs) and "hypokalaemia (severe AEs)". There is a hint of greater harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

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

The overall analysis showed both positive and negative effects of pembrolizumab + radiochemotherapy in comparison with radiochemotherapy.

In terms of positive effects, there is a hint of a non-quantifiable added benefit for the outcome of overall survival. In contrast, there are hints of greater harm with the extents “minor” to “considerable” for several outcomes in the category of serious/severe side effects.

The advantage in the outcome of overall survival dominates in the assessment of the added benefit, but is relativised by the disadvantages in the side effects, particularly severe AEs.

In summary, for patients with locally advanced cervical carcinoma (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy, there is a hint of a non-quantifiable added benefit of pembrolizumab in combination with radiochemotherapy (percutaneous radiotherapy followed by brachytherapy) compared with the ACT.

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

Table 3 shows a summary of probability and extent of the added benefit of pembrolizumab in combination with radiochemotherapy.

Table 3: Pembrolizumab + radiochemotherapy[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Adults with locally advanced cervical cancer (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy	Radiochemotherapy consisting of EBRT in combination with cisplatin (monotherapy), followed by brachytherapy	Hint of non-quantifiable added benefit[c]

a. EBRT followed by brachytherapy.
b. Presentation of the ACT specified by the G-BA.
c. Only patients with an ECOG PS of 0 or 1 were included in the KEYNOTE A18 study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; EBRT: external beam radiotherapy; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of pembrolizumab in combination with radiochemotherapy (EBRT followed by brachytherapy) compared with the ACT in patients with locally advanced cervical cancer (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy.

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

Table 4: Research question of the benefit assessment of pembrolizumab in combination with radiochemotherapy[a]

Therapeutic indication	**ACT[b]**
Adults with locally advanced cervical cancer (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy	Radiochemotherapy consisting of EBRT in combination with cisplatin (monotherapy), followed by brachytherapy
a. EBRT followed by brachytherapy. b. Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; EBRT: external beam radiotherapy; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee	

The company deviates from the G-BA's ACT in that it names cisplatin combination chemotherapy as an option as a chemotherapy component of radiochemotherapy in addition to cisplatin monotherapy. This has no consequences for the benefit assessment, as the company presented no data on this additionally named option. The benefit assessment was conducted in comparison with the ACT specified by the G-BA (see Section I 3.1).

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab (status: 4 October 2024)
- bibliographical literature search on pembrolizumab (last search on 30 September 2024)
- search in trial registries/trial results databases for studies on pembrolizumab (last search on 30 September 2024)
- search on the G-BA website for pembrolizumab (last search on 30 September 2024)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 28 November 2024); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. radiochemotherapy[a]

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)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication (yes/no [citation])
ENGOT-cx11/GOG-3047 (KEYNOTE A18[d])	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [4,7]

a. EBRT followed by brachytherapy.
b. Study for which the company was sponsor.
c. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
d. In the following tables, the study is referred to with this designation.

EBRT: external beam radiotherapy; RCT: randomized controlled trial

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a]

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE A18	RCT, double-blind, placebo-controlled	Adult patients ▪ with locally advanced high-risk cervical cancerc (stage IB2 to IIB [nodal-positive] or stage III to IVA [nodal-positive or nodal-negative] according to FIGO 2014) ▪ no prior definitive therapy ▪ ECOG PS 0 or 1	Pembrolizumab + radiochemotherapy[a] (N = 529) placebo + radiochemotherapy[a] (N = 531) relevant subpopulation thereof[d]: pembrolizumab + radiochemotherapy[a] (N = 296) placebo + radiochemotherapy[a] (N = 305)	Screening: up to 42 days treatment: pembrolizumab/placebo for a maximum of 20 cycles[e] or until disease progression, unacceptable toxicity, or study discontinuation due to the decision of the investigator or the patient, or occurrence of another malignant disease observation[f]: outcome-specific, at most until death, withdrawal of consent or end of study	154 study centres in: Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Czech Republic, France, Germany, Great Britain, Greece, Hungary, Guatemala, Ireland, Israel, Italy, Japan, Norway, Peru, Russia, Spain, Sweden, South Korea, Taiwan, Thailand, Turkey, Ukraine, USA 05/2020–ongoing data cut-offs[g]: 09 January 2023[h] 08 January 2024[f]	Primary: PFS, overall survival secondary: morbidity, health-related quality of life; AEs

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
c. Radiologically evaluable, histologically confirmed squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma.
d. Patients in stage III to IVA (nodal-positive or nodal-negative) according to FIGO 2014.
e. 5 cycles, cycle duration 3 weeks (simultaneously with radiochemotherapy), followed by 15 cycles, cycle duration 6 weeks.
f. Outcome-specific information is provided in Table 8.
g. Final data cut-off: event-driven, after approximately 240 events in the outcome of overall survival.
h. Prespecified 1st interim analysis: after completion of recruitment and approximately 237 PFS events, approximately 28 months after randomization of the first patient.
i. Prespecified 2nd interim analysis: after about 304 PFS events, about 34 months after randomization of the 1st patient.

AE adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FIGO: International Federation of Gynecology and Obstetrics; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a] (multipage table)

Study	Intervention	Comparison
KEYNOTE A18	Pembrolizumab 200 mg IV (5 cycles, every 3 weeks) + radiochemotherapy: ▪ cisplatin 40 mg/m² BSA[b] IV weekly, 5 administrations[c, d] ▪ EBRT[e], followed by brachytherapy[f, g] ▪ followed by: pembrolizumab 400 mg IV (15 cycles, every 6 weeks)	Placebo IV (5 cycles, every 3 weeks) + radiochemotherapy: ▪ cisplatin 40 mg/m² BSA[b] IV weekly, 5 administrations[c, d] ▪ EBRT[e], followed by brachytherapy[f, g] ▪ followed by: placebo i.v. (15 cycles, every 6 weeks)
	Treatment adjustment ▪ pembrolizumab/placebo: ▪ no dose adjustment ▪ interruption of up to 12 weeks for immune-related AEs ▪ cisplatin: ▪ dose reduction to 30 mg/m² BSA due to toxicity ▪ interruption due to toxicity according to local standard ▪ radiotherapy: ▪ interruption of up to 21 days due to toxicity ▪ delay in the start of brachytherapy up to 14 days after completion of EBRT ▪ if the study medication is interrupted, the radiotherapy can be continued. ▪ if EBRT is interrupted, cisplatin treatment is interrupted until EBRT is resumed.	
	Disallowed pretreatment ▪ hysterectomy in the sense of removal of the entire uterus, or as part of an initial treatment for cervical cancer ▪ systemic immunostimulants, colony-stimulating factors, interferons, interleukins and vaccine combinations within 6 weeks or 5 half-lives of the drugs before the start of treatment ▪ anti-PD-1 or anti-PD-L1/L2 drugs, or drugs directed against other stimulating or co-inhibitory T-cell receptors ▪ systemic anti-tumour therapy within 4 weeks before randomization ▪ investigational products or investigational drugs within 4 weeks prior to randomization ▪ chronic systemic steroid therapy (> 10 mg prednisone equivalent per day) or any other form of immunosuppressive therapy within 7 days before the first dose of the study medication	

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a] (multipage table)

Study	Intervention	Comparison
	Disallowed concomitant treatments: ▪ antineoplastic systemic chemotherapies or biologic therapies ▪ other immunotherapies, chemotherapies, radiosensitizers, test substances or radiotherapiesh ▪ simultaneous intake of nephrotoxic or ototoxic drugs and cisplatin ▪ live vaccines within 30 days before and up to 30 days after the end of the study treatment ▪ systemic glucocorticoids for purposes other than symptomatic treatment and prevention of AEs ▪ other use of glucocorticoids, except topical use, ophthalmic use, intra-articular joint injection, or inhalation for asthma or COPD	

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. According to local practice, the dose could be limited to 70 mg.
c. According to local practice, an optional 6th infusion could be given.
d. Cisplatin administration on a day of EBRT, prior to radiation; no cisplatin administration on days on which brachytherapy takes place.
e. 23-28 fractions within 40 days.
f. After completion of EBRT; a total treatment duration (EBRT + brachytherapy) of 50 days (at most 56 days in case of unforeseeable delays) should not be exceeded.
g. Total dose (EBRT + brachytherapy) of at least 80 Gy EQD2 for volume-based and at least 75 Gy EQD2 for point-based application. Study centres in Japan were able to follow local guidelines and administer a lower total radiation dose if necessary.
h. Exception: palliative radiotherapy of symptomatic lesions after progression has been detected.

AE: adverse event; BSA: body surface area; COPD: chronic obstructive pulmonary disease; EQD2: equivalence dose of 2 Gy; IV: intravenous; PD-1: programmed cell death-1; PD-L1/L2: PD-L1/L2: programmed cell death ligand 1/2; Q3W: every 3 weeks; Q6W: every 6 weeks; RCT: randomized controlled trial

Study design

KEYNOTE A18 is an ongoing, double-blind RCT comparing pembrolizumab + radiochemotherapy versus placebo + radiochemotherapy. In each case, radiochemotherapy consisted of EBRT in combination with cisplatin, followed by brachytherapy. The study included adult patients with locally advanced high-risk cervical cancer, defined as stage IB2 to IIB (nodal-positive) or stage III to IVA (nodal-positive or nodal-negative) according to FIGO 2014, who had not received prior definitive therapy. Patients also had to be in good general condition corresponding to an ECOG PS of 0 or 1.

A total of 1060 patients were included and randomly assigned in a 1:1 ratio to either treatment with pembrolizumab + radiochemotherapy (N = 529) or placebo + radiochemotherapy (N = 531). Randomization was stratified by the planned type of EBRT (intensity-modulated radiotherapy [IMRT]/volumetric modulated arc therapy vs. non IMRT/-VMAT), disease stage at screening (stage IB2 to IIB [nodal-positive] vs. stage III to IVA [nodal-negative or nodal-

positive] according to FIGO 2014) and planned total radiation dose from EBRT + brachytherapy (< 70 Gy vs. ≥ 70 Gy).

After completion of the recruitment of the global cohort described above, additional patients were to be randomized in China according to the study protocol until the number of study participants meets local regulatory requirements. According to the study design, these study participants are not included in the primary analysis population of the study. The Chinese cohort will then be analysed separately according to local specifications. The company presents neither results nor further information on the recruitment scope or on planned data cut-offs for the Chinese cohort. No further information can be found in the study documents either.

Only the subpopulation of patients in stage III to IVA according to FIGO 2014 is relevant for the present benefit assessment. These were 296 patients in the intervention arm and 305 patients in the comparator arm. In Module 4 A of the dossier, the company presented results for this subpopulation. These are used for the benefit assessment.

Treatment with pembrolizumab + radiochemotherapy in the intervention arm and placebo + radiochemotherapy in the comparator arm was largely carried out in accordance with the specifications of the SPC [8,9] and the recommendations of the current S3 guideline "Diagnosis, Treatment and Follow-up of Patients with Cervical Cancer" [10]. For treatment with cisplatin as part of radiochemotherapy, 5 cycles were planned in the study protocol, with an optional 6th cycle according to local practice. According to the SPC, cisplatin should be administered for 6 cycles. However, the treatment regimen planned in the study is in line with the recommendations of the S3 guideline [10]. Therefore, the deviation from the SPC remains without consequence.

With regard to radiotherapy, the procedure in the KEYNOTE A18 study deviates from the guideline recommendations in 2 points. According to the study protocol, other procedures were also permitted for EBRT in addition to IMRT and VMAT recommended by the S3 guideline. However, in the KEYNOTE A18 study, more than 85% of patients received IMRT or VMAT (see Table 9). The minimum radiation dose planned in the study protocol (total dose from EBRT and brachytherapy) of 70 Gy to 80 Gy is below the dose of 85 Gy recommended by the guideline. However, the median total radiation dose actually administered to the patients during the course of the study was approx. 87 Gy in both study arms (see Table 9). Hence, neither of the two deviations had any consequences for the benefit assessment.

Primary outcomes of the KEYNOTE A18 study are "PFS" and "overall survival". Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Data cut-offs

The KEYNOTE A18 study is an ongoing study. So far, 2 data cut-offs are available:

- First data cut-off (09 January 2023): prespecified interim analysis after completion of recruitment and approximately 237 events in the outcome of PFS
- Second data cut-off (8 January 2024): prespecified interim analysis after approx. 304 events in the outcome of PFS.

The more recent 2nd data cut-off is relevant for the present benefit assessment. The company also uses this data cut-off to derive the added benefit. The final data cut-off for the analysis of overall survival is still pending and is to take place after around 240 events in the outcome of overall survival.

Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a]

Study **outcome category** **outcome**	**Planned follow-up observation**
KEYNOTE A18	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study[b], whichever is first
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-CX24), health status (EQ-5D VAS)	Until disease progression, death, withdrawal of consent or loss to follow-up, whichever is first
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-CX24	Until disease progression, death, withdrawal of consent or loss to follow-up, whichever is first
Side effects	
AEs/severe AEs[c]	Until 30 days after the last dose of the study medication
SAEs	Until 90 days after the last dose of the study medication or 30 days in case of initiation of a subsequent antineoplastic therapy

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. According to the study protocol, the study is terminated as soon as the last patient has completed the last study-related contact, has withdrawn consent, or is lost to follow-up.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.

AE: adverse event; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The observation periods for the outcomes on symptoms, health status and health-related quality of life are systematically shortened because they were only recorded until disease progression. The outcomes in the side effects category were only recorded for the period of treatment with the study medication (plus 30 or 90 days), so that the observation times for these outcomes were also systematically shortened. However, drawing a reliable conclusion on the total study period or the time until patient death would require obtaining data regarding these outcomes throughout the entire period, as was done for survival.

Patient characteristics

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

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a] (multipage table)

Study characteristic category	Pembrolizumab + radiochemotherapy[a] N[b] = 296	Placebo + radiochemotherapy[a] N[b] = 305
KEYNOTE A18		
Age [years]		
Mean (SD)	51 (12)	52 (12)
ECOG PS at baseline, n (%)		
0	194 (66)	212 (70)
1	102 (35)	93 (31)
Disease duration: time from first diagnosis to randomization [months], mean (SD)	ND	ND
Family origin, n (%)		
Asian	104 (35)	99 (33)
Indigenous population of North America, Alaska, Hawaii or other Pacific islands	22 (7)[c]	21 (7)[c]
Black or African American	6 (2)	3 (< 1)
White	104 (35)	113 (37)
Several[d]	60 (20)	69 (23)
Lymph nodes affected, n (%)		
Positive pelvic and/or para-aortic	213 (72)	212 (70)
Neither positive pelvic nor para-aortic	83 (28)	93 (31)
Histology subtype, n (%)		
Squamous	244 (82)	258 (85)
Non-squamous	52 (18)	47 (15)
PD-L1 status[e], n (%)		
CPS < 1	14 (5)	20 (7)
CPS ≥ 1	278 (94)	281 (92)
Missing	4 (1)	4 (1)

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a] (multipage table)

Study characteristic category	**Pembrolizumab + radiochemotherapy[a] N[b] = 296**	**Placebo + radiochemotherapy[a] N[b] = 305**
Duration of radiotherapy treatment (days)		
Mean (SD)	54.5 (9.8)	54.0 (12.8)
Median [Q1; Q3]	52.0 [49.0; 57.0]	52.0 [49.5; 57.0]
Planned total radiation dose (EQD2), n (%)		
< 70 Gy	32 (11)	29 (10)
≥ 70 Gy	264 (89)	276 (91)
Total radiation dose (cervix EQD2) in Gy		
Mean (SD)	85.1 (12.1)	83.8 (15.3)
Median [Q1; Q3]	87.3 [82.8; 91.5]	87.3 [83.0; 91.8]
Planned type of EBRT, n (%)		
Intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT)	255 (86)	264 (87)
Non-IMRT/VMAT	41 (14)	41 (13)
Type of brachytherapy, n (%)		
High dose rate (HDR)	282 (95)	285 (93)
Pulsed dose rate (PDR)/low-dose-rate (LDR)	4 (1)	0 (0)
Not initiated	10 (3)	20 (7)
Treatment discontinuation, n (%)[f]	117 (40)	142 (47)
Study discontinuation, n (%)[g]	53 (18)	79 (26)

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Institute's calculation.
d. Information provided by the company.
e. Test used: PD-L1 IHC 22C3 pharmDx (Agilent Technologies) [7].
f. Common reasons for treatment discontinuation in the intervention vs. the comparator arm were: radiological progression (57 vs. 94), AE (33 vs. 15), withdrawal of consent (12 vs. 17). The values are based on the number of randomized patients in the relevant subpopulation who received study medication (intervention arm: 295 vs. control arm: 304). In addition, 128 vs. 109 of the patients completed the therapy as planned.
g. A common reason for study discontinuation in the intervention vs. the control arm was: withdrawal of consent (10 versus 5). The data also include patients who died during the course of the study (intervention arm: 41 vs. control arm: 73).

CPS: combined positive score; EBRT: external beam radiotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQD2: equivalence dose of 2 Gy; f: female; FIGO: International Federation of Gynecology and Obstetrics; HDR: high dose rate; IMRT: intensity-modulated radiotherapy; LDR: low-dose-rate; m: male; n: number of patients in the category; ND: no data; PD-L1: programmed cell death ligand 1; PDR: pulse dose rate; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; VMAT: volumetric modulated arc therapy

The characteristics of the patients in the KEYNOTE A18 study were largely balanced between the 2 study arms. The mean age of the patients was 51 or 52 years and the majority had an ECOG PS of 0. The majority of patients were Asian (around 34%) or White (around 36%). More than 80% of the patients had squamous cell carcinoma and more than 90% had a PD-L1 expression CPS ≥ 1.

The median duration of radiotherapy was 52 days in both study arms and was therefore slightly longer than the total treatment duration of 45 to 50 days recommended in the S3 guideline [10]. The patients received a median total radiation dose (EBRT + brachytherapy) of approx. 87 Gy.

Information on the course of the study

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

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a]

Study **duration of the study phase** **outcome category/outcome**	**Pembrolizumab + radiochemotherapy** **N = 296**	**Placebo + radiochemotherapy** **N = 305**
KEYNOTE A18		
Treatment duration [months]		
Median [Q1; Q3]	20.0 [N D]	16.0 [N D]
Observation period [months]		
Overall survival [b]		
Median [Q1; Q3]	27.1 [N D]	25.3 [N D]
Symptoms, health status, health-related quality of life (EORTC QLQ-C30, EORTC QLQ-CX24, EQ-5D VAS)		
Median [Q1; Q3]	22.8 [N D]	17.1 [N D]
Side effects		
AEs		
Median [Q1; Q3]	20.7 [N D]	16.9 [N D]
SAEs		
Median [Q1; Q3]	21.4 [ND] D]	17.6 [N D]

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. No information is available on how the observation period was calculated.

EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; N: number of patients in the relevant subpopulation; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

In the KEYNOTE A18 study, the median treatment duration of the patients was slightly longer in the intervention arm (20.0 months) than in the comparator arm (16.0 months). One reason for this is the clear difference in the occurrence of radiological progression events that led to treatment discontinuation (57 and 94 patients respectively, see Table 9).

For the outcome of overall survival, the median observation periods were sufficiently comparable between the study arms (27.1 and 25.3 months respectively).

For all other relevant outcomes, the median observation periods are shortened compared to the outcome of overall survival. The median observation periods between the study arms for these outcomes were longer in the intervention arm than in the comparator arm.

Subsequent therapies

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

Table 11: Information on the first subsequent antineoplastic therapya – RCT, direct comparison: pembrolizumab + radiochemotherapy[b] vs. placebo + radiochemotherapy[b]

Study drug class drug	Patients with subsequent therapy, n (%)	
	pembrolizumab + radiochemotherapy N = 296	placebo + radiochemotherapy N = 305
KEYNOTE A18		
Systemic therapy	47 (15.9)	79 (25.9)[c]
Several[d]	40 (13.5)	71 (23.3)
Paclitaxel	39 (13.2)	67 (22.0)
Bevacizumab	15 (5.1)	23 (7.5)
PD-1/PDL-1 inhibitors	5 (1.7)	7 (2.3)
Pembrolizumab	4 (1.4)	7 (2.3)
Platinum compounds	41 (13.9)	66 (21.6)
Carboplatin	31 (10.5)	52 (17.0)
Cisplatin	10 (3.4)	14 (4.6)
Taxanes	3 (1.0)	7 (2.3)
Nab-paclitaxel	2 (0.7)	7 (2.3)
Topoisomerase type I (TOP1) inhibitors	1 (0.3)	2 (0.7)
Topotecan	1 (0.3)	2 (0.7)
Palliative radiotherapy[e]	3 (1.0)	10 (3.3)[c, f]

a. Events that occurred in ≥ 2 patients (irrespective of the study arm assignment).
b. EBRT in combination with cisplatin, followed by brachytherapy.
c. One patient in the comparator arm received systemic therapy in combination with palliative radiotherapy and was counted in both categories.
d. Information provided by the company.
e. Palliative radiotherapy is any radiotherapy used to control symptoms or brain metastases.
f. Institute's calculation.

n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death protein 1; PDL-1: programmed cell death ligand 1; RCT: randomized controlled trial

In the KEYNOTE A18 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. Overall, around 16% of patients in the intervention arm and around 26% in the comparator arm received at least 1 subsequent systemic antineoplastic therapy, while 1% and 3% of patients received palliative radiotherapy. In relation to the patients with disease progression (70 patients in the intervention arm vs. 111 in the comparator arm), around 71% and 79% respectively received subsequent therapy. The most frequently administered drugs were paclitaxel, bevacizumab and the platinum compounds cisplatin and carboplatin.

The subsequent therapies used are initially consistent with the recommendations of the S3 guideline "Diagnosis, Treatment and Follow-up of Patients with Cervical Cancer" from 2022,

which specifies treatment with cisplatin or carboplatin in combination with paclitaxel and bevacizumab as a possible therapy for patients with recurrent, persistent or metastatic cervical cancer [10]. However, in relation to the patients who were treated with subsequent systemic therapy, only around 30% of patients in both study arms received bevacizumab and were therefore not treated with the triple combination recommended in the S3 guideline. However, as the combination with bevacizumab leads to an increased rate of side effects [10], it is understandable that this treatment was not an option for all patients. Therefore, no consequences arise for the benefit assessment.

With the approval of pembrolizumab in combination with chemotherapy with or without bevacizumab, a further treatment option for the first-line treatment of persistent, recurrent or metastatic cervical cancer with PD-L1-expressing tumours (CPS ≥ 1) was initially approved by the Food and Drug Administration (FDA) in October 2021, and then by the European Commission in April 2022. 'The pivotal study KEYNOTE 826 showed a clear survival benefit of this combination over chemotherapy alone (possibly in combination with bevacizumab). Based on the IQWiG assessment, the G-BA decided that this treatment option has a considerable added benefit [11,12]. However, pembrolizumab was only used in a few patients in the present study KEYNOTE A18. Although the tumours expressed PD-L1 in more than 90% of patients, only around 9% (in relation to those patients in the comparator arm who were treated with subsequent systemic therapy) received pembrolizumab. In a more recent international guideline from 2024, pembrolizumab is already recommended as one of the preferred options for patients with persistent, recurrent or metastatic cervical cancer with PD-L1-expressing tumours [13,14]. The combination with pembrolizumab was only approved after the start (May 2020) of the ongoing KEYNOTE A18 study. However, the company did not make any adjustments to the study protocol that would have provided for the possibility of switching patients in the comparator arm to combination treatment with pembrolizumab.

The results of the outcome of overall survival are decisively influenced by the subsequent antineoplastic therapies used after discontinuation of the study treatment. It must be assumed that a relevant proportion of patients would have benefited from the use of the new pembrolizumab combination therapy. This is taken into account in the assessment of the outcome-specific risk of bias and the determination of the extent of the added benefit (see Section I 4.2 and Section I 5.1).

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 + radiochemotherapy[a] vs. placebo + radiochemotherapy[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE A18	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. EBRT in combination with cisplatin, followed by brachytherapy.

AE: adverse event; EBRT: external beam radiotherapy; RCT: randomized controlled trial

The risk of bias across outcomes was rated as low for the KEYNOTE A18 study.

Transferability of the study results to the German health care context

In the company's opinion, the results of the KEYNOTE A18 study are transferable to the German health care context. The majority of patients in the stage III to IVA subpopulation (FIGO 2014) received radiochemotherapy in accordance with the recommendations of the national S3 guideline and the most common procedure in everyday health care in Germany [15-17]. The other demographic and disease-specific characteristics of the patients are also comparable with the German target population.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms
    - recorded with the EORTC QLQ-C30
    - recorded with the EORTC QLQ CX24
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
  - recorded using the EORTC QLQ-CX24
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related severe AEs
  - other 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 are available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a]

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]	Immune-related severe AEs[c, d]	Further specific AEs[e]
KEYNOTE A18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. Progression events of the underlying disease are not included (PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression").
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Version 23.1 of the PT list of immune-related adverse events predefined by the company is used.
e. The following events (MedDRA coding) are considered: anaemia (PT, SAEs), hypokalaemia (PT, severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Notes on outcomes

Overall survival

An observed effect in the outcome of overall survival is not only influenced by the initial study treatment, but also by the subsequent therapies used after treatment discontinuation. The meaningful interpretation of an observed effect in the outcome of overall survival therefore requires adequate subsequent treatment of patients after discontinuation of study treatment.

As described in Section I 3.2, the relevant subpopulation of the KEYNOTE A18 study was found to have deficiencies with regard to the subsequent therapies used. Due to the size of the effect in the outcome of overall survival, it is nevertheless considered to be interpretable to a limited extent; the extent of the added benefit is considered as non-quantifiable due to the uncertainties described.

Failure of the curative treatment approach

Radiochemotherapy is a curative treatment approach in the present therapeutic indication. Failure to achieve remission or recurrence of the disease after achieved remission means that the curative treatment approach has failed in this line of therapy. Failure of the curative treatment approach is a patient-relevant event in this therapeutic indication, as it is usually followed by a transition to a palliative treatment situation. Failure of the curative treatment approach is therefore considered a patient-relevant outcome in this assessment.

A mandatory requirement for the operationalization of this outcome is the determination that the patient is tumour-free during or after potentially curative therapy, i.e. at a time when it can be assumed that the therapy has been successful. Failure to achieve tumour-free status at this point in time and the occurrence of recurrences at a point in time after tumour-free status has been established means that the curative treatment approach can be assumed to have failed.

The analyses presented by the company are not suitable to depict the outcome failure of the curative treatment approach. In Module 4 A, the company presents analyses on PFS. In the KEYNOTE A18 study, PFS was operationalized as the time from randomization to disease progression or death from any cause, whichever occurred first. Disease progression was analysed by the investigator based on a radiological event according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 or an optional biopsy for histopathological confirmation in case of suspected disease progression.

The analyses presented by the company on the outcome of PFS only depict those events in which disease progression according to RECIST criteria occurred during observation. A statement on whether and how many of the patients in the study population achieved a tumour-free status is not possible on the basis of the analyses presented by the company. Thus, the operationalization presented by the company is therefore unsuitable for depicting the failure of the curative treatment approach.

In addition, the observation period in the KEYNOTE A18 study at the time of the 2nd data cut-off used for the benefit assessment is too short to cover the occurrence of events leading to failure of the curative approach in all patients. Recurrences usually occur in the first 5 years after radiochemotherapy, mostly within the first 2 to 3 years after primary therapy [10,18-20]. In the present data cut-off, the median observation period was just over 2 years (see Table 10, based on overall survival) and is also only slightly longer than the median treatment duration until the completion of the monotherapy phase with pembrolizumab.

In summary, the outcome of failure of the curative treatment approach is not used for the benefit assessment in the present operationalization.

Symptoms, health status, and health-related quality of life

EORTC QLQ-C30, EORTC QLQ-CX24, EQ-5D VAS

For the outcomes of symptoms, health status and health-related quality of life, recorded using the EORTC QLQ-C30, EORTC QLQ-CX24 and EQ-5D VAS, the company presented analyses for the mean change between baseline and the last time point at which the response rates were at least 60% (this time point was pre-specified and was reached at Week 60). The calculation was carried out using Constrained Longitudinal Data Analysis (cLDA). These analyses were used for the benefit assessment. In principle, responder analyses are also possible for these outcomes, which would be preferable according to the IQWiG *General Methods* [1].

Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change of Sleep Disturbance (PGI-C SD)

In Module 4 A, the company presents results of the patient-reported single-item scales PGI-S and PGI-C. However, there is no information on the wording of the items in the study documents. Therefore, the patient relevance of the outcomes recorded with the PGI-S and PGI-C cannot be assessed. The results of the PGI-S and the PGI-C are therefore not used for the benefit assessment. Regardless of this, the results show no statistically significant differences between the study arms for either the PGI-S or the PGI-C.

Side effects

In the consideration of side effects, the number of patients in whom an event occurred is primarily relevant. The relative risk is the appropriate effect measure for these analyses. In event time analyses with the hazard ratio as an effect measure, however, effects can also result from an earlier or later occurrence of the event, and not on the basis of the proportions. However, there are situations with different observation durations between the study arms in which the relative risk is not suitable and event time analyses should be presented instead [1]. For the outcomes in the side effects category, the company presented analyses on the proportion of patients with an event for which the relative risk is specified as an effect measure. However, as there is a relevant difference between the median observation periods in the intervention and the comparator arm (see Table 10), the relative risk can only be interpreted to a limited extent. Event time analyses with hazard ratio as an effect measure would therefore be the appropriate analyses according to the module template. Despite the uncertainties arising from the consideration of the relative risk, in the present situation of an add-on therapy in the intervention arm, these are considered to be sufficiently interpretable, e.g. to detect significant effects with regard to side effects that are characteristic of pembrolizumab treatment according to the SPC (see Table 15). Therefore, the analyses presented by the company are nevertheless used for the benefit assessment.

Immune-related AEs

In Module 4 A, the company presents analyses on immune-related AEs of special interest. In doing so, the immune-related AEs are determined using a predefined but regularly updated PT collection. This operationalization is deemed a sufficient approximation for immune-related AEs. The company only presented analyses of the overall rates, but not a presentation of the results at the level of PTs or SOCs.

I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] vs. placebo + radiochemotherapy[a]

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 AEsb	Immune-related severe AEs[c, d]	Further specific AEs[e]
KEYNOTE A18	L	H[f]	L	L	L	H[g]	H[g]	L[h]	H[g]	H[g]

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. Progression events of the underlying disease are not included (PTs “neoplasm progression”, “malignant neoplasm progression” and “disease progression”).
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. Version 23.1 of the PT list of immune-related adverse events predefined by the company is used.
e. The following events (MedDRA coding) are considered: anaemia (PT, SAEs), hypokalaemia (PT, severe AEs).
f. Due to uncertainties in the use of adequate subsequent therapies.
g. Incomplete observations for potentially informative reasons with different follow-up observation periods.
h. Despite the low risk of bias, the certainty of results for the outcome “discontinuation due to AEs” was assumed to be limited (see running text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-CX24: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

For the results on the outcome of overall survival, the risk of bias is rated as high. Uncertainties in the administered subsequent therapies are decisive for the high risk of bias (see Section I 3.2 and Section I 4.1).

The outcome-specific risk of bias for the results of the patient-reported outcomes on symptoms, health status and health-related quality of life, recorded using the EORTC QLQ-C30, EORTC QLQ-CX24 and EQ-5D VAS, is classified as low in each case.

The outcome-specific risk of bias was rated as high for the results on the outcomes of the side effects category except for the outcome of discontinuation due to AEs. This is due to incomplete observations for potentially informative reasons with different median observation durations. These result from the fact that the recording of side effects is linked to the end of the study treatment and the median treatment duration of the patients in the intervention arm was longer than in the comparator arm (see Table 8 and Table 10).

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

I 4.3 Results

Table 15 and Table 16 summarize the results on the comparison of pembrolizumab + radiochemotherapy with placebo + radiochemotherapy in patients with locally advanced cervical cancer (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier. An SMD is used to assess clinical relevance in the case of a statistically significant mean difference.

Kaplan-Meier curves on the time-to-event analysis of the outcome of overall survival 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. A list of the occurred immune-related AEs, immune-related SAEs and severe immune-related AEs (CTCAE grade ≥ 3) by SOC, PT or grouped by category is not available.

Table 15: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] versus placebo + radiochemotherapy[a]

Study outcome category outcome	Pembrolizumab + radiochemotherapy		Placebo + radiochemotherapy		Pembrolizumab + radiochemotherapy vs. placebo + radiochemotherapy
	N	patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[b]
KEYNOTE A18					
Mortality					
Overall survival	296	43 (14.5) median time to event: NA	305	73 (23.9) median time to event: NA	HR: 0.57 [0.39; 0.83][c]; 0.004[c, d]
Side effects					
AEs (supplementary information)[e]	295	295 (100.0)	304	302 (99.3)	–
SAEs[e]	295	100 (33.9)	304	99 (32.6)	1.04 [0.83; 1.31]; 0.776
Severe AEs[e, f]	295	232 (78.6)	304	213 (70.1)	1.12 [1.02; 1.23]; 0.017
Discontinuation due to AEs[e]	295	62 (21.0)	304	46 (15.1)	1.39 [0.98; 1.96]; 0.063
Immune-related severe AEs[f, g]	295	12 (4.1)	304	4 (1.3)	3.09 [1.01; 9.48]; 0.037
Anaemia (PT, SAEs)	295	13 (4.4)	304	3 (1.0)	4.47 [1.29; 15.51]; 0.010
Hypokalaemia (PT, severe AEs[f])	295	22 (7.5)	304	10 (3.3)	2.27 [1.09; 4.71]; 0.024

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. For the outcomes of the categories "morbidity" and "side effects": Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [21]).
c. Cox proportional hazards model.
d. Wald test (two-sided).
e. Progression events of the underlying disease are not included (PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression").
f. Operationalized as CTCAE grade ≥ 3.
g. Determined using Version 23.1 of a PT list of immune-related adverse events predefined by the company is used.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] versus placebo + radiochemotherapy[a] (multipage table)

Study outcome category outcome	Pembrolizumab + radiochemotherapy			Placebo + radiochemotherapy			Pembrolizumab + radiochemotherapy vs. placebo + radiochemotherapy
	N[b]	values at baseline mean (SD)	mean change in the course of the study mean (95% CI)[d]	N[b]	values at baseline mean (SD)	mean change in the course of the study mean (95% CI)[d]	MD [95% CI]; p-value[d]
KEYNOTE A18							
Morbidity							
Symptoms (EORTC QLQ-C30)[e]							
Fatigue	272	30.4 (24.8)	-7.9 [-11.0; -4.8]	283	30.1 (22.9)	-8.3 [-11.4; -5.2]	0.41 [-3.62; 4.45]; 0.841
Nausea and vomiting	272	8.6 (16.1)	-3.0 [-4.9; -1.1]	283	8.2 (17.6)	-3.7 [-5.7; -1.8]	0.77 [-1.44; 2.99]; 0.492
Pain	272	35.9 (32.1)	-17.1 [-20.6; -13.5]	283	33.3 (28.5)	-14.9 [-18.6; -11.2]	-2.16 [-6.74; 2.41]; 0.353
Dyspnoea	272	10.0 (19.0)	-1.3 [-3.6; 1.1]	283	8.9 (18.0)	-1.6 [-4.0; 0.8]	0.33 [-2.56; 3.22]; 0.822
Insomnia	272	30.8 (30.6)	-12.5 [-16.3; -8.8]	283	31.6 (30.0)	-12.1 [-15.9; -8.2]	-0.45 [-5.19; 4.28]; 0.851
Appetite loss	272	19.3 (25.8)	-9.2 [-12.3; -6.1]	283	21.2 (28.3)	-11.9 [-15.0; -8.7]	2.62 [-0.99; 6.24]; 0.155
Constipation	272	23.4 (29.7)	-13.8 [-17.2; -10.4]	283	24.2 (29.6)	-11.1 [-14.5; -7.6]	-2.72 [-6.75; 1.32]; 0.186
Diarrhoea	272	5.4 (15.9)	4.9 [2.2; 7.6]	283	6.4 (16.5)	1.1 [-1.7; 3.9]	3.83 [0.27; 7.38]; 0.035 SMD: 0.22 [0.02; 0.42]
Symptoms (EORTC QLQ-C30)[e]							
Symptom experience	272	20.6 (14.7)	-10.7 [-12.5; -9.0]	281	21.1 (15.7)	-10.8 [-12.5; -9.1]	0.06 [-2.04; 2.15]; 0.958
Lymphoedema	272	4.0 (12.3)	1.7 [-0.8; 4.1]	281	6.7 (17.7)	1.6 [-0.9; 4.1]	0.06 [-3.16; 3.28]; 0.970
Peripheral neuropathy	272	9.8 (18.1)	7.7 [4.2; 11.2]	281	10.9 (20.9)	4.7 [1.2; 8.3]	2.99 [-1.61; 7.58]; 0.203
Menopausal symptoms	272	16.9 (24.8)	2.6 [-1.4; 6.6]	281	17.0 (24.8)	2.0 [-2.1; 6.0]	0.67 [-4.47; 5.81]; 0.798
Sexual/vaginal functioning	No usable data[f]						
Health status (EQ-5D VAS)[g]	272	72.0 (21.3)	9.5 [7.1; 11.9]	281	70.2 (20.1)	7.8 [5.4; 10.2]	1.68 [-1.31; 4.67]; 0.270

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] versus placebo + radiochemotherapy[a] (multipage table)

Study outcome category outcome	Pembrolizumab + radiochemotherapy			Placebo + radiochemotherapy			Pembrolizumab + radiochemotherapy vs. placebo + radiochemotherapy
	N[b]	values at baseline mean (SD)	mean change in the course of the study mean (95% CI)[d]	N[b]	values at baseline mean (SD)	mean change in the course of the study mean (95% CI)[d]	MD [95% CI]; p-value[d]
Health-related quality of life							
EORTC QLQ-C30[g]							
Global health status	272	64.5 (23.7)	10.3 [7.4; 13.2]	283	64.1 (21.9)	9.3 [6.3; 12.2]	1.01 [-2.58; 4.60]; 0.581
Physical functioning	272	83.8 (18.2)	4.8 [2.5; 7.0]	283	83.4 (18.0)	5.2 [2.9; 7.4]	-0.42 [-3.25; 2.42]; 0.772
Role functioning	272	78.7 (27.2)	5.2 [2.0; 8.5]	283	79.1 (26.0)	6.1 [2.8; 9.4]	-0.88 [-5.01; 3.25]; 0.675
Emotional functioning	272	73.4 (21.9)	9.9 [7.1; 12.7]	283	72.8 (21.9)	5.4 [2.6; 8.3]	4.50 [0.78; 8.23]; 0.018 SMD: 0.24 [0.04; 0.43]
Cognitive functioning	272	84.4 (20.9)	-0.1 [-2.9; 2.6]	283	87.4 (18.7)	-2.0 [-4.7; 0.8]	1.83 [-1.71; 5.36]; 0.310
Social functioning	272	80.7 (23.7)	6.1 [3.1; 9.1]	283	78.0 (24.3)	5.8 [2.8; 8.8]	0.34 [-3.43; 4.10]; 0.861
EORTC QLQ-CX24[g]							
Sexual activity	No usable data[h]						
Worries about dyspareunia	No usable data[h]						
Sexual enjoyment	No usable data[f]						
Body image	No usable data[h]						

Table 16: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + radiochemotherapy[a] versus placebo + radiochemotherapy[a] (multipage table)

Study outcome category outcome	Pembrolizumab + radiochemotherapy			Placebo + radiochemotherapy			Pembrolizumab + radiochemotherapy vs. placebo + radiochemotherapy
	N[b]	values at baseline mean (SD)	mean change in the course of the study mean (95% CI)[d]	N[b]	values at baseline mean (SD)	mean change in the course of the study mean (95% CI)[d]	MD [95% CI]; p-value[d]

a. EBRT in combination with cisplatin, followed by brachytherapy.
b. Number of patients taken into account in the effect estimation; values at baseline and in the course of the study may rest on different patient numbers.
c. The period between the start of the study and Week 60 is considered.
d. The constrained longitudinal data analysis (cLDA) model with PRO value as dependent variable and treatment-visit interaction as covariate.
e. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
f. According to the company, only values from patients who were documented as sexually active according to the EORTC QLQ-CX24 functional scale "sexual activity" were included. Due to the small number of patients considered, it was not possible to conduct analyses using the cLDA model.
g. Higher (increasing) values indicate a better health status/health-related quality of life; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).
h. Presented analyses of the sexual activity scale are not plausible: The company states in Module 4 A that only a few patients were sexually active. However, the data presented indicate a high level of sexual activity. The analyses of the scales "worries about dyspareunia" and "body image" are also not considered to be plausible. Regardless of this, there were no significant differences between the study arms.

CI: confidence interval; cLDA: constrained longitudinal data analysis; EORTC QLQ-CX24: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; MD: mean difference; N: number of analysed patients; PRO: patient-reported outcome; RCT: randomized controlled trial; SD: standard deviation; SMD: standardized mean difference; VAS: visual analogue scale

Based on the available information, at most indications can be determined for the patient-reported outcomes on symptoms, health status and health-related quality of life (recorded using the EORTC QLQ-C30, EORTC QLQ-CX24 and EQ-5D VAS) and at most hints, e.g. of an added benefit, can be determined for overall survival and for the outcomes in the side effects category due to the high risk of bias.

Mortality

Overall survival

For the outcome "overall survival", a statistically significant difference was found in favour of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

There is a hint of added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

Morbidity

Symptoms

EORTC QLQ-C30 (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea)

No statistically significant difference between the study arms was shown for any of the outcomes “fatigue”, “nausea and vomiting”, “pain”, “dyspnoea”, “insomnia”, “appetite loss” and “constipation”. In each case, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

For the outcome of diarrhoea, a statistically significant difference was found to the disadvantage of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. There is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

EORTC QLQ-CX24 (symptom experience, lymphoedema, peripheral neuropathy, menopausal symptoms and sexual/vaginal functioning)

No statistically significant difference between the study arms was found for any of the outcomes of symptom experience, lymphoedema, peripheral neuropathy or menopausal symptoms. In each case, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

No usable data are available for the outcome of sexual/vaginal functioning. Therefore, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

Health status

EQ-5D VAS

There was no statistically significant difference between study arms for the outcome of EQ-5D VAS. There is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (global health status, physical functioning, role functioning, cognitive functioning, social functioning and emotional functioning)

No statistically significant difference between the study arms was shown for any of the following outcomes: global health status, physical functioning, role functioning, cognitive functioning and social functioning. In each case, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

For the outcome “emotional functioning”, a statistically significant difference was found in favour of pembrolizumab + radiochemotherapy versus placebo + radiochemotherapy. The SMD is analysed to examine the relevance of the result. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effect can therefore not be inferred to be relevant. There is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; an added benefit is therefore not proven.

EORTC QLQ-CX24 (sexual activity, worries about painful intercourse, sexual enjoyment and body image)

There are no usable data available for each of the outcomes of sexual activity, worries about dyspareunia, sexual enjoyment and body image. Therefore, there is no hint of an added benefit of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy in any case; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, there is no statistically significant difference between the study arms. There is no hint of greater or lesser harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy was shown for the outcome of severe AEs (CTCAE grade ≥ 3). There is a hint of greater harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

Discontinuation due to AEs

There was no statistically significant difference between the study arms for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from pembrolizumab +

radiochemotherapy in comparison with placebo + radiochemotherapy; greater or lesser harm is therefore not proven.

Immune-related severe AEs (CTCAE grade ≥ 3), anaemia (SAEs) and hypokalaemia (severe AEs)

A statistically significant difference to the disadvantage of pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy was shown for each of the outcomes “immune-related severe AEs” (CTCAE grade ≥ 3)”, “anaemia” (SAEs) and "hypokalaemia (severe AEs)". There is a hint of greater harm from pembrolizumab + radiochemotherapy in comparison with placebo + radiochemotherapy.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristic was considered in the present benefit assessment:

- Age (< 65 years versus ≥ 65 years)

This subgroup characteristic was predefined in the KEYNOTE A18 study, but only for the outcomes of overall survival and PFS.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Applying the methods described above, there were no relevant effects for the benefit assessment.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 17).

Table 17: Extent of added benefit at outcome level: pembrolizumab + radiochemotherapy[a] vs. radiochemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + radiochemotherapy vs. radiochemotherapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	NA vs. NA HR: 0.57 [0.39; 0.83]; p = 0.004 probability: “hint”	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: “non-quantifiable”
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)		
Fatigue	-7.9 vs. -8.3 MD: 0.41 [-3.62; 4.45] p = 0.841	Lesser/added benefit not proven
Nausea and vomiting	-3.0 vs. -3.7 MD: 0.77 [-1.44; 2.99] p = 0.492	Lesser/added benefit not proven
Pain	-17.1 vs. -14.9 MD: -2.16 [-6.74; 2.41] p = 0.353	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab + radiochemotherapy[a] vs. radiochemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + radiochemotherapy vs. radiochemotherapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Dyspnoea	-1.3 vs. -1.6 MD: 0.33 [-2.56; 3.22] p = 0.822	Lesser/added benefit not proven
Insomnia	-12.5 vs. -12.1 MD: -0.45 [-5.19; 4.28] p = 0.851	Lesser/added benefit not proven
Appetite loss	-9.2 vs. -11.9 MD: 2.62 [-0.99; 6.24] p = 0.155	Lesser/added benefit not proven
Constipation	-13.8 vs. -11.1 MD: -2.72 [-6.75; 1.32] p = 0.186	Lesser/added benefit not proven
Diarrhoea	4.9 vs. 1.1 MD: 3.83 [0.27; 7.38]; p = 0.035 SMD: 0.22 [0.02; 0.42][c]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-CX24)		
Symptom experience	-10.7 vs. -10.8 MD: 0.06 [-2.04; 2.15] p = 0.958	Lesser/added benefit not proven
Lymphoedema	1.7 vs. 1.6 MD: 0.06 [-3.16; 3.28] p = 0.970	Lesser/added benefit not proven
Peripheral neuropathy	7.7 vs. 4.7 MD: 2.99 [-1.61; 7.58] p = 0.203	Lesser/added benefit not proven
Menopausal symptoms	2.6 vs. 2.0 MD: 0.67 [-4.47; 5.81] p = 0.798	Lesser/added benefit not proven
Sexual/vaginal functioning	No usable data	Lesser/added benefit not proven
Health status		
EQ-5D VAS	9.5 vs. 7.8 MD: 1.68 [-1.31; 4.67] p = 0.270	Lesser/added benefit not proven

Table 17: Extent of added benefit at outcome level: pembrolizumab + radiochemotherapy[a] vs. radiochemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + radiochemotherapy vs. radiochemotherapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
EORTC QLQ-C30		
Global health status	10.3 vs. 9.3 MD: 1.01 [-2.58; 4.60] p = 0.581	Lesser/added benefit not proven
Physical functioning	4.8 vs. 5.2 MD: -0.42 [-3.25; 2.42] p = 0.772	Lesser/added benefit not proven
Role functioning	5.2 vs. 6.1 MD: -0.88 [-5.01; 3.25] p = 0.675	Lesser/added benefit not proven
Emotional functioning	9.9 vs. 5.4 MD: 4.50 [0.78; 8.23]; p = 0.018 SMD: 0.24 [0.04; 0.43][c]	Lesser/added benefit not proven
Cognitive functioning	-0.1 vs. -2.0 MD: 1.83 [-1.71; 5.36] p = 0.310	Lesser/added benefit not proven
Social functioning	6.1 vs. 5.8 MD: 0.34 [-3.43; 4.10] p = 0.861	Lesser/added benefit not proven
EORTC QLQ-CX24		
Sexual activity	No usable data	Lesser/added benefit not proven
Worries about dyspareunia	No usable data	Lesser/added benefit not proven
Sexual enjoyment	No usable data	Lesser/added benefit not proven
Body image	No usable data	Lesser/added benefit not proven
Side effects		
SAEs	33.9% vs. 32.6% RR: 1.04 [0.83; 1.31]; p = 0.776	Greater/lesser harm not proven
Severe AEs	78.6 % vs. 70.1 % RR: 1.12 [1.02; 1.23] RR: 0.89 [0.81; 0.98][f] p < 0.017 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”

Table 17: Extent of added benefit at outcome level: pembrolizumab + radiochemotherapy[a] vs. radiochemotherapy[a] (multipage table)

Outcome category **outcome**	**Pembrolizumab + radiochemotherapy vs. radiochemotherapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability[b]**	**Derivation of extent[c]**
Discontinuation due to AEs	21.0% vs. 15.1% RR: 1.39 [0.98; 1.96]; p = 0.063	Greater/lesser harm not proven
Immune-related severe AEs	4.1 % vs. 1.3 % RR: 3.09 [1.01; 9.48] RR: 0.32 [0.11; 0.99][f] p < 0.037 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: minor
Anaemia (SAEs)	4.4 % vs. 1.0 % RR: 4.47 [1.29; 15.51] RR: 0.22 [0.06; 0.78][e] p = 0.010 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Hypokalaemia (severe AEs)	7.5 % vs. 3.3 % RR: 2.27 [1.09; 4.71] RR: 0.44 [0.21; 0.92][e] p = 0.024 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: minor

a. EBRT followed by brachytherapy.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category and the scale of the outcome, effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_l).
d. See Section I 3.2 and Section I 4.2 for a rationale.
e. If the CI for the SMD is fully outside the irrelevance range [-0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-EORTC QLQ-CX24: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cervical Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HR: hazard ratio; MD: mean difference; RR: relative risk; SAE: serious adverse; SMD: standardized mean difference; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 18 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of pembrolizumab + radiochemotherapy[a] in comparison with radiochemotherapy[a]

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival: hint of an added benefit – extent: “non-quantifiable”	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: “minor” ▪ immune-related severe AEs: hint of greater harm – extent "minor" ▪ anaemia (SAEs): hint of greater harm – extent: “considerable” ▪ hypokalaemia (severe AEs): hint of greater harm – extent: “minor”
a. EBRT followed by brachytherapy. AE: adverse event; EORTC QLQ-CX24: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cervical Cancer Module; SAE: serious adverse event	

The overall analysis showed both positive and negative effects of pembrolizumab + radiochemotherapy in comparison with radiochemotherapy.

In terms of positive effects, there is a hint of a non-quantifiable added benefit for the outcome of overall survival. In contrast, there are hints of greater harm with the extents “minor” to “considerable” for several outcomes in the category of serious/severe side effects.

The advantage in the outcome of overall survival dominates in the assessment of the added benefit, but is relativised by the disadvantages in the side effects, particularly severe AEs.

In summary, for patients with locally advanced cervical carcinoma (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy, there is a hint of a non-quantifiable added benefit of pembrolizumab in combination with radiochemotherapy (percutaneous radiotherapy followed by brachytherapy) compared with the ACT.

Table 19 summarizes the result of the assessment of added benefit of pembrolizumab in combination with radiochemotherapy versus the ACT.

Table 19: Pembrolizumab + radiochemotherapy[a] – probability and extent of added benefit

Therapeutic indication	**ACT[b]**	**Probability and extent of added benefit**
Adults with locally advanced cervical cancer (stage III to IVA according to FIGO 2014) who have not received prior definitive therapy	Radiochemotherapy consisting of EBRT in combination with cisplatin (monotherapy), followed by brachytherapy	Hint of non-quantifiable added benefitc

a. EBRT followed by brachytherapy.
b. Presentation of the ACT specified by the G-BA.
c. Only patients with an ECOG PS of 0 or 1 were included in the KEYNOTE A18 study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; EBRT: external beam radiotherapy; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; FIGO: International Federation of Gynecology and Obstetrics; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which derived an indication of major added benefit.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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