# Pembrolizumab (cervical cancer)

## Addendum to Project A22-70 (dossier assessment)[1]

**ADDENDUM**

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

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

**IQWiG employees involved in the addendum**

- Isabelle Paulußen
- Merlin Bittlinger
- Ana Liberman
- Daniela Preukschat
- Katherine Rascher

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## List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| CPS | combined positive score |
| EORTC | European Organisation for Research and Treatment of Cancer |
| 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 |
| QLQ-C30 | Quality of Life Questionnaire – Core 30 |
| QLQ-CX24 | Quality of Life Questionnaire – Cervical Cancer Module |

# 1 Background

On 21 December 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-70 (Pembrolizumab – Benefit assessment according to § 35a Social Code Book V) [1].

The ordered commission comprises the assessment of the analyses subsequently submitted by the company on time until the 1st clinically relevant deterioration by ≥ 10 points each in the scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire – Cervical Cancer Module (EORTC QLQ-CX24) from the KEYNOTE 826 study.

The assessment was conducted in consideration of the information provided in the dossier [2].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

# 2 Assessment

To answer research question 1 (patients with persistent, recurrent, or metastatic cervical cancer; first line), benefit assessment A22-70 [1] used the KEYNOTE 826 study investigating the added benefit of pembrolizumab in combination with chemotherapy with or without bevacizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with persistent, recurrent, or metastatic cervical cancer with tumours expressing programmed cell death ligand 1 (PD-L1) (combined positive score [CPS] ≥ 1). The KEYNOTE 826 study compared pembrolizumab + chemotherapy ± bevacizumab versus placebo + chemotherapy ± bevacizumab. In both study arms, chemotherapy consisted of the drug combinations of either cisplatin + paclitaxel or carboplatin + paclitaxel. Therefore, this study is suitable for drawing conclusions on added benefit only for pembrolizumab + chemotherapy ± bevacizumab in the patient group for which cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab represents a suitable treatment of physician's choice. No data are available for patients who are candidates for other treatment options of physician's choice. A detailed description of the KEYNOTE 826 study can be found in the benefit assessment on commission A22-70 [1].

For the patient-reported outcomes of the categories morbidity and health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-CX24), the company's dossier presents analyses of time to 1st clinically relevant deterioration by ≥ 15 points each from the KEYNOTE 826 study.

## 2.1 Analyses of symptoms (EORTC QLQ-C30, EORTC QLQ-CX24) and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-CX24)

For the patient-reported outcomes of the categories morbidity and health-related quality of life, the company presented in the commenting procedure analyses of time to 1st clinically relevant deterioration by ≥ 10 points each in the KEYNOTE 826 study's scales of the EORTC QLQ-C30 and the EORTC QLQ-CX24 [3]. According to the "Answers to frequently asked questions about the benefit assessment procedure" [4] provided by the G-BA, only analyses using the currently accepted minimal important difference (MID) of 10 points are to be presented in the dossier for analyses of the EORTC QLQ-C30 questionnaire and the corresponding validated supplementary disease-specific modules. The analyses on the response threshold of 10 points are relevant for the dossier assessment and were used.

The available responder analyses allow drawing conclusions only for the shortened observation period. This is due to the fact that the observation period for the patient-reported outcomes on symptoms and health-related quality of life is shortened when compared to overall survival, as described in dossier assessment A22-70.

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.

Module 4A and the documents supplied with the comments provide no information on the duration of follow-up observation for these outcomes. Module 4A presents the return rates for all questionnaires only for the treatment duration (up to Week 99). In its comments, the company did not provide any other information on this topic. It therefore remains unclear whether the available responder analyses account for surveys conducted for follow-up observation. In principle, the entire observation period, including all follow-up observations, must be included in the analysis.

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

### 2.1.1 Risk of bias

The risk of bias was rated as high for the results on the outcomes of symptoms (EORTC QLQ-C30, EORTC QLQ-CX24) and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-CX24). 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.

According to dossier assessment A22-70, a minimum of 35.9% (maximum of 38.5%) of the relevant subpopulation did not receive any combination therapy with bevacizumab despite the fact that, in the present therapeutic indication, simultaneous administration of bevacizumab is indicated as per the S3 guideline [5]. The study documents provided neither the reasons why the investigator deemed add-on bevacizumab treatment not to be medically indicated nor criteria underlying the treatment decision. It therefore remained unclear whether all patients not receiving combination therapy with bevacizumab were in fact not medically indicated for bevacizumab. This resulted in reduced certainty of conclusions for all outcomes, irrespective of risk of bias-related aspects.

The company's comments provide the reasons for the decision against additional treatment with bevacizumab [3]. Accordingly, in 74.4% of patients who did not receive bevacizumab (28.6% of the relevant subpopulation), the treatment decision was based on the benefit-risk profile. In 8.5% of patients not treated with bevacizumab (3.3% of the relevant subpopulation), the decision was based on medical reasons which were not further specified, and 17.1% of patients without bevacizumab treatment (6.6% of the relevant subpopulation) failed to receive bevacizumab due to a lack of availability, approval, or investigator experience. These data show that few patients in the relevant subpopulation received no bevacizumab for nonmedical reasons such as unavailability. In view of the subsequently submitted data, this

aspect is therefore not expected to affect the certainty of conclusions of the study results. Based on the available information, at most hints, e.g. of an added benefit, can be derived for the outcomes of symptoms (EORTC QLQ-C30, EORTC QLQ-CX24) and health-related quality of life (EORTC QLQ-C30, EORTC QLQ-CX24) due to high risk of bias. Unlike in dossier A22-70, however, at most an indication, e.g. of an added benefit, can be derived for the outcome of overall survival, which is associated with a low risk of bias.

### 2.1.2 Results

Table 1 presents the results for the outcomes of symptoms and health-related quality of life.

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation)(multipage table)

| **Study**<br>**Outcome category**<br>**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]**<br>**Patients with event n (%)** | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]; p-value[b]** |
| **KEYNOTE 826** | | | | | |
| **Morbidity** | | | | | |
| Symptoms (EORTC QLQ-C30; time to 1st deterioration by ≥ 10 points)[c] | | | | | |
| Fatigue | 246 | 1.4 [1.4; 2.1]<br>199 (80.9) | 253 | 2.0 [1.4; 2.2]<br>189 (74.7) | 1.12 [0.92; 1.37]; 0.257 |
| Nausea and vomiting | 246 | 2.9 [2.4; 3.7]<br>170 (69.1) | 253 | 2.7 [2.1; 3.9]<br>171 (67.6) | 0.99 [0.80; 1.22]; 0.912 |
| Pain | 246 | 4.5 [3.4; 5.8]<br>155 (63.0) | 253 | 3.4 [2.3; 4.7]<br>164 (64.8) | 0.94 [0.76; 1.18]; 0.607 |
| Dyspnoea | 246 | 3.6 [2.8; 4.6]<br>164 (66.7) | 253 | 6.2 [3.6; 8.3]<br>140 (55.3) | 1.30 [1.03; 1.63]<br>0.025 |
| Insomnia | 246 | 5.5 [3.7; 7.6]<br>141 (57.3) | 253 | 6.3 [4.9; 8.7]<br>137 (54.2) | 1.08 [0.85; 1.36]; 0.544 |
| Appetite loss | 246 | 5.5 [4.2; 8.3]<br>144 (58.5) | 253 | 5.9 [4.5; 7.6]<br>139 (54.9) | 0.99 [0.78; 1.25]; 0.925 |
| Constipation | 246 | 4.1 [2.2; 6.9]<br>142 (57.7) | 253 | 4.7 [3.0; 7.0]<br>148 (58.5) | 0.99 [0.78; 1.25]; 0.924 |
| Diarrhoea | 246 | 4.2 [2.9; 7.0]<br>146 (59.3) | 253 | 6.5 [4.9; 9.9]<br>131 (51.8) | 1.21 [0.95; 1.54]; 0.116 |

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation)(multipage table)

| **Study**<br>**Outcome category**<br>**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]**<br>**Patients with event n (%)** | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]; p-value[b]** |
| Symptoms (EORTC QLQ-CX24; time to 1st deterioration by ≥ 10 points)[c] | | | | | |
| Symptom experience | 244 | NR<br>81 (33.2) | 251 | NR [12.6; NC]<br>88 (35.1) | 0.80 [0.59; 1.09]; 0.152 |
| Lymphoedema | 244 | 9.7 [6.3; 17.4]<br>123 (50.4) | 251 | 11.1 [6.2; NC]<br>112 (44.6) | 1.06 [0.82; 1.37]; 0.654 |
| Peripheral neuropathy | 244 | 1.4 [1.0; 1.6]<br>207 (84.8) | 251 | 1.7 [1.4; 2.1]<br>197 (78.5) | 1.22 [1.00; 1.49]; 0.049 |
| Menopausal symptoms | 244 | 5.5 [3.0; 9.1]<br>134 (54.9) | 251 | 6.9 [5.0; 12.1]<br>126 (50.2) | 1.14 [0.89; 1.46]; 0.285 |
| Sexual/vaginal functioning[d] | No suitable data[e] | | | | |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30 (time to 1st deterioration by ≥ 10 points)[f] | | | | | |
| Global health status | 246 | 4.1 [3.1; 6.3]<br>156 (63.4) | 253 | 3.5 [2.8; 4.6]<br>172 (68.0) | 0.85 [0.68; 1.06]; 0.149 |
| Physical functioning | 246 | 3.4 [2.8; 4.1]<br>171 (69.5) | 253 | 3.5 [3.0; 4.8]<br>166 (65.6) | 1.09 [0.88; 1.36]; 0.414 |
| Role functioning | 246 | 2.1 [1.5; 2.9]<br>189 (76.8) | 253 | 2.8 [2.1; 3.3]<br>188 (74.3) | 1.00 [0.81; 1.23]; 0.983 |
| Emotional functioning | 246 | 6.9 [5.4; 12.9]<br>130 (52.8) | 253 | 7.0 [5.7; 13.9]<br>128 (50.6) | 1.02 [0.80; 1.31]; 0.860 |
| Cognitive functioning | 246 | 2.8 [2.1; 3.8]<br>180 (73.2) | 253 | 3.5 [2.8; 4.4]<br>166 (65.6) | 1.10 [0.89; 1.36]; 0.394 |
| Social functioning | 246 | 2.8 [2.1; 4.1]<br>173 (70.3) | 253 | 3.5 [2.7; 4.2]<br>163 (64.4) | 1.12 [0.90; 1.39]; 0.322 |

Table 1: Results (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + chemotherapy[a] ± bevacizumab versus placebo + chemotherapy[a] ± bevacizumab (relevant subpopulation)(multipage table)

| **Study**<br>**Outcome category**<br>**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]**<br>**Patients with event n (%)** | **N** | **Median time to event in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]; p-value[b]** |
| EORTC QLQ-CX24 (time to 1st deterioration by ≥ 10 points)[f] | | | | | |
| Sexual activity | 236 | NR<br>41 (17.4) | 248 | NR<br>33 (13.3) | 1.16 [0.73; 1.85]; 0.520 |
| Worries about dyspareunia, sexual activity, and intimacy[g] | 234 | NR<br>73 (31.2) | 244 | NR [16.3; NC]<br>65 (26.6) | 1.02 [0.73; 1.43]; 0.918 |
| Sexual enjoyment | No suitable data[e] | | | | |
| Body image | 244 | 3.0 [2.0; 4.2]<br>157 (64.3) | 251 | 2.2 [1.5; 3.3]<br>169 (67.3) | 0.91 [0.73; 1.13]; 0.394 |

a. Paclitaxel + cisplatin or paclitaxel + carboplatin.
b. Effect, CI, and p-value: Cox proportional hazards model; for outcomes of the categories morbidity and health-related quality of life, stratified by metastasis, PD-L1 status, and investigator's decision regarding bevacizumab use.
c. A score increase by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 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. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range of 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.

CI: confidence interval; 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; HR: hazard ratio; 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; RCT: randomized controlled trial

**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 ≥ 10 points (scale range 0 to 100) was analysed.

*EORTC QLQ-C30*

*Dyspnoea*

For the outcome of dyspnoea, a statistically significant difference was found between treatment groups to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. However, this difference is no more than marginal (i.e. the upper limit of the confidence interval is above 0.90; outcome category of non-serious/non-severe symptoms / late complications as in A22-70). 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, the treatment groups exhibited a statistically significant difference to the disadvantage of pembrolizumab + chemotherapy ± bevacizumab in comparison with placebo + chemotherapy ± bevacizumab. However, this difference is no more than marginal (i.e. the upper limit of the confidence interval is above 0.90; outcome category of non-serious/non-severe symptoms / late complications as in A22-70). 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 suitable 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-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 ≥ 10 points (scale range 0 to 100) was analysed.

***EORTC QLQ-C30***

*Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning*

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, 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, worries about dyspareunia, sexual activity, and intimacy, sexual enjoyment, body image*

No statistically significant difference between treatment groups was found for any of the outcomes of sexual activity, worries about dyspareunia, sexual activity, and intimacy, or body image. No suitable 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.

### 2.1.3 Subgroups and other effect modifiers

The company has not submitted any subgroup analyses on the subsequently submitted analyses.

In the overall consideration of results, the missing subgroup analyses do not appear to impact the overall conclusion on added benefit in a relevant way.

### 2.1.4 Probability and extent of added benefit

#### 2.1.4.1 Assessment of added benefit at outcome level

Because the subsequently submitted analyses each result in no hint of an added or lesser benefit, the extent of added benefit at outcome level is not presented in table form. In each case, the added benefit is not proven.

#### 2.1.4.2 Overall conclusion on added benefit

Table 2 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 2: 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<br>▪ Overall survival: indication of added benefit – extent: major | – |
| **Shortened observation period** | |
| – | Serious/severe side effects<br>▪ Immune-mediated SAEs: hint of greater harm – extent: minor<br>▪ Immune-mediated severe AEs: hint of greater harm – extent major<br>▪ Skin and subcutaneous tissue disorders (severe AEs): hint of greater harm – extent: major |
| – | Non-serious/non-severe side effects<br>▪ Discontinuation due to AEs: hint of greater harm – extent: minor |
| a. Paclitaxel + cisplatin or paclitaxel + carboplatin.<br>AE: adverse event; SAE: serious adverse event | |

Overall, the subsequently assessed results show no effects other than those presented in dossier assessment A22-70. While the subsequently submitted data lack subgroup analyses, this shortcoming does not appear to impact the overall conclusion on added benefit in a relevant manner in the overall analysis of results. Unlike in dossier assessment A22-70, however, an indication rather than a hint of major added benefit results for the outcome of overall survival.

Overall, there is an indication 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.

## 2.2 Summary

The data subsequently submitted by the company in the commenting procedure change the conclusion on the added benefit of pembrolizumab from dossier assessment A22-70 regarding research question 1: for patients with persistent, recurrent, or metastatic cervical cancer (first line) for whom cisplatin + paclitaxel ± bevacizumab or carboplatin + paclitaxel ± bevacizumab represented suitable ACT options upon the physician's choice, taking into account the

subsequently submitted data results in an indication of major added benefit of pembrolizumab versus the ACT. In dossier assessment A22-70, only a hint of major added benefit was found for this research question because it was unclear whether all patients not receiving bevacizumab combination therapy were generally not indicated for bevacizumab. This uncertainty was adequately cleared by the data subsequently submitted in the comments.

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

For research question 2, there is no change from dossier assessment A22-70.

Table 3 below shows the result of the benefit assessment of pembrolizumab, taking into account dossier assessment A22-70 and the present addendum.

Table 3: Pembrolizumab + chemotherapy ± bevacizumab – probability and extent of added benefit (multipage table)

| **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] | Treatment of physician's choice[c] | ▪ Patients for whom cisplatin or carboplatin + paclitaxel ± bevacizumab is a suitable therapy of physician's choice: indication of major added benefit[d]<br>▪ 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 | Treatment of physician's choice[f] | Added benefit not proven |

Table 3: Pembrolizumab + chemotherapy ± bevacizumab – probability and extent of added benefit (multipage table)

| Research question | Therapeutic indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| a. Presented is the respective ACT specified by the G-BA.<br>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.<br>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).<br>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.<br>e. No prior systemic chemotherapy except when used as a radiosensitizer.<br>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).<br>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 G-BA decides on the added benefit.

## 3 References

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