IQWiG Reports – Commission No. A19-101

# Pembrolizumab (head and neck squamous cell carcinoma, combination with chemotherapy) –

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

## Extract

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

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| 5-FU | 5-fluorouracil |
| ACT | appropriate comparator therapy |
| AE | adverse event |
| CPS | combined positive score |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EQ-5D | European Quality of Life-5 Dimensions |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| HNSCC | head and neck squamous cell carcinoma |
| HPV | human papillomavirus |
| IHC | immunohistochemistry |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| ITT | intention to treat |
| PD-1 | programmed cell death 1 |
| PD-L1 | programmed cell death ligand 1 |
| PFS | progression-free survival |
| PT | Preferred Term |
| QLQ-C30 | Quality of Life Questionnaire-Cancer 30 |
| QLQ-H&N35 | Quality of Life Questionnaire-Head and Neck Cancer 35 |
| RCT | randomized controlled trial |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| TPS | Tumour Proportion Score |
| VAS | visual analogue scale |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 December 2019.

### Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with carboplatin + 5-fluorouracil (5-FU) or cisplatin + 5-FU in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS) ≥ 1.

The G-BA's specification of the ACT resulted in the research question presented in the following Table 2.

Table 2: Research question of the benefit assessment of pembrolizumab + chemotherapy[a]

| **Therapeutic indication** | **ACT[b]** |
|---|---|
| First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1[c] | **Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU**<br>*or*<br>radiochemotherapy with cisplatin ± 5-FU<br>(only for patients with locally advanced head and neck squamous cell carcinoma)<br>*or*<br>cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy<br>(only for patients with locally advanced head and neck squamous cell carcinoma) |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. For the present therapeutic indication, it is assumed that in this patient group an intervention with curative intent is an exception and therefore no longer indicated. The G-BA also assumes that only patients whose disease progression did not occur within 6 months of completion of prior therapy with curative intent are eligible for platinum-containing therapy [1].

5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

Following the G-BA's specification, the company named cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU as comparator therapy. Hereinafter, the comparator therapy is referred to as "cetuximab + chemotherapy", and the intervention with pembrolizumab + carboplatin + 5-FU or pembrolizumab + cisplatin + 5-FU is referred to as "pembrolizumab + chemotherapy".

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) were used for the derivation of the added benefit.

**Results**

***Study pool and study characteristics***

The study KEYNOTE-048 was included for the benefit assessment. This is an ongoing, open-label, randomized, active-controlled multicentre study.

Adults with metastatic or unresectable recurrent HNSCC considered incurable by local therapies were enrolled in the study. Furthermore, the patients included had not received any prior systemic therapy in the recurrent or metastatic setting, and hence were in first-line treatment (for the advanced disease stage) in the study. A further inclusion criterion was that tumour progression did not occur within 6 months of completion of prior therapy with curative intent for locally advanced tumour. In addition, prior curatively intended systemic therapies (therapies for locally advanced tumour) had to be completed ≥ 6 months before the start of the study.

281 (pembrolizumab+ chemotherapy) and 300 (cetuximab + chemotherapy) patients were randomly allocated to the study arms relevant for the present benefit assessment. Of these patients, the subpopulation of patients whose tumours express PD-L1 with a CPS ≥ 1 is relevant (242 in the pembrolizumab + chemotherapy arm and 235 in the cetuximab + chemotherapy arm in the intention to treat (ITT) analysis; 237 in the pembrolizumab + chemotherapy arm versus 245 in the cetuximab + chemotherapy arm in the analyses of adverse events [AEs]).

Therapy in the KEYNOTE-048 study was largely in compliance with the Summaries of Product Characteristics (SPCs). The drugs pembrolizumab and cetuximab could be given for a maximum of 24 months in the study; treatment with carboplatin, cisplatin and 5-FU was given for a maximum of 6 cycles of 3 weeks each.

Primary outcomes of the KEYNOTE-048 study were "progression-free survival (PFS)" and "overall survival". Outcomes on morbidity, health-related quality of life and AEs were recorded as patient-relevant secondary outcomes.

***Risk of bias***

The risk of bias across outcomes was rated as low for the KEYNOTE-048 study. The outcome-specific risk of bias was rated as high for the results of all outcomes. For the outcome "overall

survival", the reason for this is that not all patients in the comparator arm may have had access to PD-L1 therapies as subsequent therapy due to the different standards of care in the different countries of the international study. Thus, the comparison of the treatment arms carry a risk of bias in favour of the pembrolizumab arm. The risk of bias for the results of symptom outcomes recorded with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Cancer 30 (QLQ-C30) and Head and Neck Cancer 35 (QLQ-H&N35) was rated as high due to the lack of blinding in subjective recording of outcomes and due to incomplete observations for potentially informative reasons. The risk of bias of the results for the outcome "health status" (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]) was rated as high due to the lack of blinding in subjective recording of outcomes due to the large proportion of patients not included in the analysis. The risk of bias for the results of health-related quality of life outcomes recorded with the EORTC QLQ-C30 and QLQ-H&N35 was rated as high due to the lack of blinding in subjective recording of outcomes and due to incomplete observations for potentially informative reasons. For all outcomes of the outcome category of side effects, the high risk of bias was due to the fact that there were incomplete observations for potentially informative reasons due to the large proportions of patients who discontinued treatment and the lack of blinding in subjective recording of outcomes (does not apply to all side effect outcomes). Furthermore, there were no survival time analyses for Preferred Terms (PTs) and the different observation periods between control and intervention arm therefore resulted in an additional high risk of bias in the analyses used (based on the number of patients with at least one event).

Based on the available data, no more than hints, e.g. of an added benefit, can generally be determined for all outcomes. Due to the size of the effect, the outcome-specific certainty of the results may not be downgraded.

***Mortality***

*Overall survival*

A statistically significant difference in favour of pembrolizumab was shown for the outcome "overall survival". This resulted in a hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT.

***Morbidity***

*Symptoms (EORTC QLQ-C30)*

*Fatigue*

No statistically significant difference between the treatment groups was shown for the outcome "fatigue". There was an effect modification for the characteristic "sex", however. For men, the effect modification resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group. For women, this resulted in a hint of lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT.

*Insomnia*

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus the ACT was shown for the outcome "insomnia". The effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

*Nausea and vomiting, pain, dyspnoea, appetite loss, constipation and diarrhoea*

There were no statistically significant differences between the treatment groups for each of the following outcomes: nausea and vomiting, pain, dyspnoea, appetite loss, constipation, and diarrhoea. In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

*Symptoms (EORTC QLQ-H&N35)*

*Pain*

No statistically significant difference between the treatment groups was shown for the outcome "pain". There was an effect modification for the characteristic "disease status", however. The effect modification resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients with metastatic disease. A statistically significant difference in favour of pembrolizumab + chemotherapy versus the ACT was shown for patients with (unresectable) recurrent disease. The effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

*Dry mouth*

No statistically significant difference between the treatment groups was shown for the outcome "dry mouth". There was an effect modification for the characteristic "smoking status", however. A statistically significant difference in favour of pembrolizumab + chemotherapy versus the ACT was shown for patients who were former or never smokers. The effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT for this patient group; an added benefit is therefore not proven for this patient group. For patients who are active smokers, there was also no hint of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

*Feeling ill*

No statistically significant difference between the treatment groups was shown for the outcome "feeling ill". There was an effect modification for the characteristic "sex", however. For men, the effect modification resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for

this patient group. For women, this resulted in a hint of lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT.

*Problems with swallowing, senses, speech, teeth, mouth opening, sticky saliva and coughing*

No statistically significant differences between the treatment groups were shown for any of the following outcomes: problems with swallowing, senses, speech, teeth, mouth opening, sticky saliva and coughing. In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

*Health status (EQ-5D VAS)*

The outcome "health status" was recorded with the EQ-5D VAS. In the present benefit assessment, the analysis was conducted as change at week 9 from baseline. There was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

***Health-related quality of life***

*EORTC QLQ-C30 (functional scales and global health status scale)*

*Physical functioning*

There was no statistically significant difference between the treatment groups for the outcome "physical functioning". There was an effect modification for the characteristic "age", however. The effect modification resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients under the age of 65 years. For patients aged 65 years or older, there was no hint of lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

*Cognitive functioning*

There was no statistically significant difference between the treatment groups for the outcome "cognitive functioning". There was an effect modification for the characteristic "sex", however. For men, the effect modification resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group. For women, this resulted in a hint of lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT.

*Global health status, role functioning, emotional functioning and social functioning*

No statistically significant differences between the treatment groups were shown for the outcomes "global health status", "role functioning", "emotional functioning" and "social functioning". In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

*EORTC QLQ-H&N35 (functional scales)*

*Problems with social eating*

No statistically significant difference between the treatment groups was shown for the outcome "problems with social eating". There was an effect modification for the characteristic "age", however. The effect modification resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients under the age of 65 years. For patients aged 65 years or older, there was no hint of lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

*Problems with social contact and reduced sexuality*

No statistically significant differences between the treatment groups were shown for the outcomes "problems with social contact" and "reduced sexuality". In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

***Side effects***

*Serious adverse events*

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy was shown for the outcome "serious adverse events (SAEs)". This resulted in a hint of greater harm from pembrolizumab + chemotherapy in comparison with the ACT.

*Severe adverse events (CTCAE grade ≥ 3)*

No statistically significant difference between the treatment groups was shown for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)". This resulted in no hint of greater or lesser harm of pembrolizumab + chemotherapy versus the ACT cetuximab + chemotherapy; greater or lesser harm is therefore not proven.

*Discontinuation due to adverse events*

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of pembrolizumab + chemotherapy versus the ACT cetuximab + chemotherapy; greater or lesser harm is therefore not proven.

*Specific adverse events*

*Immune-related serious adverse events*

No statistically significant difference between the treatment groups was shown for the outcome "immune-related SAEs". This resulted in no hint of greater or lesser harm of pembrolizumab + chemotherapy versus the ACT cetuximab + chemotherapy; greater or lesser harm is therefore not proven.

*Immune-related severe adverse events (CTCAE grade ≥ 3)*

A statistically significant difference in favour of pembrolizumab + chemotherapy was shown for the outcome "immune-related severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab + chemotherapy in comparison with the ACT.

*Paronychia*

A statistically significant difference in favour of pembrolizumab + chemotherapy was shown for the outcome "paronychia". Despite the high risk of bias, the certainty of results was not downgraded in this outcome. This resulted in an indication of lesser harm from pembrolizumab + chemotherapy in comparison with the ACT.

*Skin and subcutaneous tissue disorders (CTCAE grade ≥ 3)*

A statistically significant difference in favour of pembrolizumab + chemotherapy was shown for the outcome "skin and subcutaneous tissue disorders (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab + chemotherapy in comparison with the ACT.

*Anaemia (CTCAE grade ≥ 3), stomatitis (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3) and respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)*

Statistically significant differences to the disadvantage of pembrolizumab + chemotherapy in comparison with cetuximab + chemotherapy were shown for the following outcomes: anaemia (CTCAE grade ≥ 3), stomatitis (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3) and respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3). In each case, this resulted in a hint of greater harm from pembrolizumab + chemotherapy in comparison with the ACT.

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

On the basis of the results presented, probability and extent of the added benefit of pembrolizumab + chemotherapy in comparison with the ACT are assessed as follows:

Overall, partly only for subgroups, several positive and negative effects were shown, each with the probability "hint" or "indication" and with different extent.

A hint of an added benefit with the extent "major" was shown for overall survival.

[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 [2,3].

In the outcome category of serious/severe side effects, a hint of lesser harm with the extent "considerable" or "major" was shown both for immune-related severe AEs (CTCAE grade ≥ 3) and for skin and subcutaneous tissue disorders. It should be noted that there was relevant overlap between both outcomes in terms of events included. A further positive effect with the extent "considerable" was shown in the outcome category of non-serious/non-severe side effects.

The positive effects were accompanied by hints of negative effects, each with the extent "minor" or "considerable", in the overall rate of SAEs and in several specific severe AEs. It should also be noted that, for the outcome categories of morbidity and health-related quality of life, exclusively negative effects, each with the extent "minor" to "major", were shown for different subgroups. In the overall consideration, this resulted in a downgrading of the extent of the added benefit.

In summary, there is a hint of considerable added benefit of pembrolizumab + chemotherapy versus the ACT for adults with metastatic or unresectable recurrent HNSCC whose tumours express PD-L1 with a CPS ≥ 1.

Table 3 shows a summary of probability and extent of the added benefit of pembrolizumab + chemotherapy.

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

| **Therapeutic indication** | **ACT[b]** | **Probability and extent of added benefit** |
|---|---|---|
| First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1[c] | **Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU**<br>*or*<br>radiochemotherapy with cisplatin ± 5-FU<br>(only for patients with locally advanced head and neck squamous cell carcinoma)<br>*or*<br>cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy<br>(only for patients with locally advanced head and neck squamous cell carcinoma) | Hint of considerable added benefit[d] |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. For the present therapeutic indication, it is assumed that in this patient group an intervention with curative intent is an exception and therefore no longer indicated. The G-BA also assumes that only patients whose disease progression did not occur within 6 months of completion of prior therapy with curative intent are eligible for platinum-containing therapy [1].
d. The KEYNOTE-048 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. Furthermore, only patients were included who had completed a prior systemic therapy with curative intent ≥ 6 months at the start of the study and in whom progression had not occurred within 6 months of completion of prior therapy with curative intent.

5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1

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

## 2.2 Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with carboplatin + 5-FU or cisplatin + 5-FU in comparison with the ACT for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1.

The G-BA's specification of the ACT resulted in the research question presented in the following Table 4.

Table 4: Research question of the benefit assessment of pembrolizumab + chemotherapy[a]

| **Therapeutic indication** | **ACT[b]** |
|---|---|
| First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1[c] | **Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU**<br>*or*<br>radiochemotherapy with cisplatin ± 5-FU<br>(only for patients with locally advanced head and neck squamous cell carcinoma)<br>*or*<br>cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy<br>(only for patients with locally advanced head and neck squamous cell carcinoma) |
| a. Carboplatin + 5-FU or cisplatin + 5-FU.<br>b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.<br>c. For the present therapeutic indication, it is assumed that in this patient group an intervention with curative intent is an exception and therefore no longer indicated. The G-BA also assumes that only patients whose disease progression did not occur within 6 months of completion of prior therapy with curative intent are eligible for platinum-containing therapy [1].<br>5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death ligand 1 | |

Following the G-BA's specification, the company named cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU as comparator therapy. Hereinafter, the comparator therapy is referred to as "cetuximab + chemotherapy", and the intervention with pembrolizumab + carboplatin + 5-FU or pembrolizumab + cisplatin + 5-FU is referred to as "pembrolizumab + chemotherapy".

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

## 2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab + chemotherapy (status: 7 October 2019)
- bibliographical literature search on pembrolizumab + chemotherapy (last search on 7 October 2019)
- search in trial registries for studies on pembrolizumab + chemotherapy (last search on 14 October 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab + chemotherapy (last search on 5 December 2019)

No additional relevant study was identified from the check.

### 2.3.1 Studies included

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

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

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[b] (yes/no) | Third-party study (yes/no) |
| KEYNOTE-048 | Yes | Yes | No |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Study for which the company was sponsor.

5-FU: 5-fluorouracil; RCT: randomized controlled trial; vs.: versus

The study KEYNOTE-048 was used for the benefit assessment. The subpopulation of patients whose tumours express PD-L1 with a CPS ≥ 1 was considered (see Section 2.3.2). This concurs with the company's approach.

Section 2.6 contains a reference list for the studies included.

### 2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[b] |
|---|---|---|---|---|---|---|
| KEYNOTE-048 | RCT, parallel, open-label | Adults with histologically or cytologically confirmed metastatic or unresectable recurrent head and neck squamous cell carcinoma, with ECOG PS 0 or 1, without prior systemic therapy (in the advanced setting)[c] | Pembrolizumab (N = 301)[d]<br>pembrolizumab + chemotherapy[a] (N = 281)<br>cetuximab + chemotherapy[a] (N = 278[e])<br><br>Relevant subpopulation thereof/subpopulation thereof analysed by the company[f]:<br>pembrolizumab + chemotherapy[a] (n = 242)<br>cetuximab + chemotherapy[a] (n = 235[e]) | Screening: up to 28 days<br><br>Treatment: until radiological disease progression, unacceptable side effect, investi-gator's/patient's decision, at most 24 months[g, h]<br><br>Observation[i]: outcome-specific, at most until death, withdrawal of consent or end of the study | 228 study centres in:<br>Argentina, Australia, Austria, Brazil, Canada, Chile, Columbia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Peru, Philippines, Poland, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, USA<br><br>4/2015–ongoing<br>Data cut-offs:<br>Interim analysis I: 17 Oct 2017<br>Interim analysis II: 13 Jun 2018<br>Final data cut-off: 25 Feb 2019 | Primary: overall survival, PFS<br>Secondary: symptoms, health status, health-related quality of life, AEs |

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[b] |
|---|---|---|---|---|---|---|
| a. Carboplatin + 5-FU or cisplatin + 5-FU (at the investigator's discretion, determined before randomization).<br>b. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.<br>c. Systemic curatively intended therapy which was completed more than 6 months prior to signing consent if given as part of combination therapy for locally advanced disease was allowed.<br>d. The arm is not relevant for the assessment and is not shown in the next tables.<br>e. Randomization into the pembrolizumab + chemotherapy arm was interrupted from 13 August 2015 until 1 October 2015. For this reason, the company excludes 22 patients randomized into the comparator arm during this period from the ITT population for the comparison of pembrolizumab + chemotherapy vs. cetuximab + chemotherapy. However, all patients of the comparator arm (N = 300 in the total population and N = 245 in the relevant subpopulation) are included in the safety analyses.<br>f. Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1.<br>g. Patients in the pembrolizumab+ chemotherapy arm were allowed to interrupt treatment on completion of the 24-month therapy or in case of confirmed complete response, and reinitiate treatment with pembrolizumab for another year at the investigator's discretion ("second course phase") after subsequent radiologically confirmed progression (if certain conditions regarding the duration of treatment and disease status were met) if they had not received any other cancer treatment after discontinuation of the study treatment.<br>h. Treatment with chemotherapy (carboplatin + 5-FU or cisplatin + 5-FU) was conducted for a maximum of 6 cycles; treatment with cetuximab could be continued beyond these 6 cycles.<br>i. Outcome-specific information is provided in Table 8.<br>5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ITT: intention to treat; n: relevant subpopulation; N: number of randomized patients; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus | | | | | | |

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

| Study | Intervention | Comparison |
|---|---|---|
| KEYNOTE-048 | Pembrolizumab 200 mg IV every 3 weeks, for a maximum of 24 months<br>+<br>▪ cisplatin[b] 100 mg/m² BSA IV every 3 weeks, for a maximum of 6 cycles<br>*or*<br>▪ carboplatin[b] AUC 5 IV, every 3 weeks, for a maximum of 6 cycles<br>+<br>5-FU 1000 mg/m² BSA/day IV continuous infusion on days 1–4 of a cycle, every 3 weeks, for a maximum of 6 cycles | Cetuximab 400 mg/m² BSA IV (initial dose) on day 1 of the first cycle, then 250 mg/m² BSA weekly, for a maximum of 24 months<br>+<br>▪ cisplatin[b] 100 mg/m² BSA IV every 3 weeks, for a maximum of 6 cycles<br>*or*<br>▪ carboplatin[b] AUC 5 IV, every 3 weeks, for a maximum of 6 cycles<br>+<br>5-FU 1000 mg/m² BSA/day IV continuous infusion on days 1–4 of a cycle, every 3 weeks, for a maximum of 6 cycles |
| | **Dose adjustments**<br>▪ Pembrolizumab: dose adjustment not allowed, interruption or treatment discontinuation in case of AEs in compliance with the SPC | ▪ Cetuximab: dose adjustment, interruption or treatment discontinuation without relevant deviations from the SPC |
| | ▪ Carboplatin, cisplatin and 5-FU: dose adjustment, interruption or treatment discontinuation without relevant deviations from the SPC | |
| | **Pretreatment**<br><u>not allowed:</u><br>▪ systemic therapy in the metastatic or recurrent setting<br>▪ radiotherapy or other non-systemic therapy within 2 weeks prior to randomization<br>▪ investigational preparations within 4 weeks before first dose of study medication<br>▪ immunosuppressants or systemic corticosteroids within 7 days prior to the first dose of study medication (exception: corticosteroids for the treatment of allergic reactions or as prophylaxis of side effects of chemotherapy)<br>▪ prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent<br>▪ live vaccines within 30 days prior to the first dose of study medication<br><u>allowed:</u><br>▪ systemic therapy as part of combination therapy for locally advanced cancer which was completed ≥ 6 months before start of the study | |

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

| Study | Intervention | Comparison |
|---|---|---|
| | **Concomitant treatment**<br>not allowed:<br>▪ antineoplastic systemic chemotherapy or biologic therapy<br>▪ other immunotherapy or chemotherapy not conforming to the protocol<br>▪ other investigational preparations<br>▪ radiotherapy (exception: individual symptomatic lesions or brain radiation); palliative radiotherapy was analysed as clinical progression<br>▪ live vaccines (allowed in the comparator arm)<br>For patients in the intervention arm:<br>▪ systemic corticosteroids, see allowed concomitant treatment for exceptions<br>allowed:<br>▪ premedication for the platinum-based combination chemotherapy used in the study: dexamethasone ≤ 8 mg on day 1 of a cycle before study medication<br>▪ premedication for cetuximab: H1 antagonist before the first dose<br>▪ supportive treatment of immune-related side effects under pembrolizumab, e.g. corticosteroids orally or IV and other anti-inflammatory drugs, thyroid hormone substitution therapy for hypothyroidism | |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. In case of intolerance, treatment could be switched from cisplatin to carboplatin.

5-FU: 5-fluorouracil; AE: adverse event; AUC: area under the curve; BSA: body surface area; IV: intravenous; PD-1: programmed cell death 1; PD-L1/PD-L2 programmed cell death ligand 1/2; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The included KEYNOTE-048 study is an ongoing, open-label, randomized, active-controlled multicentre study.

Adults with metastatic or unresectable recurrent HNSCC considered incurable by local therapies were enrolled in the KEYNOTE-048 study. Furthermore, the patients included had not received any prior systemic therapy in the recurrent or metastatic setting, and hence were in first-line treatment (for the advanced disease stage) in the study. A further inclusion criterion was that tumour progression did not occur within 6 months of completion of prior therapy with curative intent for locally advanced tumour. In addition, prior curatively intended systemic therapies (therapies for locally advanced tumour) had to be completed ≥ 6 months before the start of the study.

281 patients were randomly allocated to treatment with pembrolizumab + chemotherapy, 301 to treatment with pembrolizumab, and 300 to treatment with cetuximab + chemotherapy. Allocation to the 3 study arms was in a ratio of 1:1:1 and was stratified according to Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 versus 1), PD-L1 status (Tumour Proportion Score [TPS] < 50% versus TPS ≥ 50%) and human papillomavirus (HPV) status (positive versus negative). However, HPV status was assessed exclusively in patients with oropharyngeal cancer (test used: p16 immunohistochemistry [IHC] using the CINtec p16

histology assay and a 70% cut-off); HPV status was assumed negative for all other locations. As planned a priori, randomization into the pembrolizumab + chemotherapy arm was interrupted from 13 August 2015 to 1 October 2015 to verify the safety of the treatment regimen, and then continued on 2 October 2015 on the recommendation of an external committee. Randomization to the other 2 study arms was continued during this time.

The study arms with pembrolizumab + chemotherapy and with cetuximab + chemotherapy were relevant for the research question of the present benefit assessment; the study arm with pembrolizumab was therefore not considered further.

Adults with metastatic or unresectable recurrent HNSCC were enrolled in the KEYNOTE-048 study, regardless of whether their tumours expressed PD-L1 or not. Due to the approval of pembrolizumab, only the subpopulation of patients whose tumours express PD-L1 with CPS $\geq 1$ is relevant for the present benefit assessment [4,5]. Due to the interrupted randomization to the pembrolizumab + chemotherapy arm (see above), the company additionally excluded those patients who were randomly allocated to the cetuximab + chemotherapy arm during this period for the formation of the relevant subpopulation for ITT analyses of mortality, morbidity and health-related quality of life. This concerned 22 patients from the comparator arm. Thus, 242 patients in the pembrolizumab + chemotherapy arm and 235 in the cetuximab + chemotherapy arm remained for these analyses of the company. The company's analyses of AEs, in contrast, included all patients whose tumours express PD-L1 with a CPS $\geq 1$ and who received the respective study medication (237 in the pembrolizumab + chemotherapy arm versus 245 in the cetuximab + chemotherapy arm).

As the deviation was only 22 patients, the company's approach was adequate; the analyses presented by the company were used for the present benefit assessment. In the following, only the relevant subpopulation will be discussed, unless otherwise stated.

Possibly deviating from the recommendations of the individual SPCs, the dosage of the individual combination partners in the cetuximab + chemotherapy arm was carried out in accordance with the dosage in the so-called EXTREME study (the approval study for the combination of cetuximab + chemotherapy [6]), which the SPC on cetuximab also refers to for the combination of cetuximab + chemotherapy [6,7]. Treatment with cetuximab + chemotherapy was therefore largely in compliance with the SPCs [6,8-10]. Treatment of the patients with pembrolizumab + chemotherapy was also largely in compliance with the SPCs [4,5,8-10]; the dosage of the chemotherapy also concurred with the dosage in the EXTREME study [7].

Primary outcomes of the KEYNOTE-048 study were PFS (described by the company as survival without cancer progression or death) and overall survival. Outcomes on morbidity, health-related quality of life and AEs were recorded as patient-relevant secondary outcomes. The individual outcomes, their patient relevance and the suitability of the presented analyses are described in Section 2.7.4.3.2 of the full dossier assessment.

**Analysis and data cut-offs**

Different data cut-offs were performed in the KEYNOTE-048 study:

- interim analysis I from 17 October 2017: prespecified analysis of the outcomes "PFS" and "overall survival"
- interim analysis II from 13 June 2018: prespecified analysis of the outcome "overall survival" and final analysis of the outcome "PFS"
- data cut-off from 25 February 2019: prespecified final analysis of overall survival; analysis of all outcomes

The final data cut-off was used in the present benefit assessment.

**Treatment duration and follow-up observation**

Treatment of the study population was until progression, occurrence of unacceptable side effects or decision by the investigator or the patient. Furthermore, treatment with pembrolizumab was given for a maximum of 24 months, whereby patients who had received pembrolizumab + chemotherapy could additionally receive a second treatment with pembrolizumab (in monotherapy) of up to 1 year if they met defined criteria, and AEs were again recorded for this "second course phase". The criteria were, for example, that patients had been treated with pembrolizumab + chemotherapy for at least 24 weeks and that (during the course of the study) there was a complete response to pembrolizumab + chemotherapy in the course of the study, assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1. This kind of therapy in the second course phase was administered to 4 patients each in the total population as well as in the relevant subpopulation. Administration of pembrolizumab monotherapy after progression is an approved subsequent therapy [4,5]. In the comparator arm, treatment with cetuximab was for at most 24 months. In both study arms, treatment with carboplatin or cisplatin and 5-FU was terminated after 6 cycles of 3 weeks at the latest, while treatment with the respective combination partner pembrolizumab or cetuximab was continued as described.

In the KEYNOTE-048 study, the occurrence of progression based on the RECIST criteria (version 1.1) was confirmed by a blinded, central review committee. In addition, there was the option of confirming disease progression after the initial diagnosis of progression by radiological reassessment (after 4 weeks at the earliest) for patients treated with pembrolizumab. In the meantime, the treating physicians could decide whether to continue or discontinue treatment with the study medication, depending on the clinical status of the patient. If the radiological reassessment showed a reduction of the tumour, treatment with pembrolizumab could be continued.

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

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

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **KEYNOTE-048** | |
| Mortality | |
| Overall survival | Up to death, withdrawal of consent or end of study, whichever is first |
| Morbidity | |
| Disease-related symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35), health status (EQ-5D VAS) | Up to 30 days after the last dose of the study medication or until 1 year of treatment initiation, whichever is first |
| Health-related quality of life<br>EORTC QLQ-C30 and EORTC QLQ-H&N35 | Up to 30 days after the last dose of the study medication or until 1 year of treatment initiation, whichever is first |
| Side effects | |
| AEs | Up to 30 days after the last dose of the study medication[b] |
| SAEs and all immune-related AEs | Up to 90 days after the last dose of the study medication[b], or 30 days after the last dose of the study medication[b] and start of subsequent therapy[b] |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. These data refer to the first course phase of the study (maximum treatment duration of 24 months), observation was resumed in the second course phase. 4 patients in the intervention arm initiated a second course phase.

5-FU: 5-fluorouracil; AE: adverse event; EORTC European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35, RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes on morbidity, health-related quality of life and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days or up to 90 days for SAEs and all immune-related AEs). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for overall survival.

### Characteristics of the relevant subpopulation

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

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| **Study Characteristics Category** | **Pembrolizumab + chemotherapy[a] N = 242** | **Cetuximab + chemotherapy[a] N = 235** |
|---|---|---|
| **KEYNOTE-048 (data cut-off: 25 February 2019)** | | |
| Age [years], mean (SD) | 61 (10) | 61 (10) |
| Sex [F/M], % | 22/78 | 14/86 |
| Family origin, n (%) | | |
| White | 178 (73.6) | 173 (73.6) |
| Non-white | 64 (26.4) | 61 (26.0) |
| Missing | 0 (0.0) | 1 (0.4) |
| Region, n (%) | | |
| North America | 53 (21.9) | 51 (21.7) |
| Europe | 76 (31.4) | 82 (34.9) |
| Rest of the world | 113 (46.7) | 102 (43.4) |
| Smoking status, n (%) | | |
| Never | 50 (20.7) | 58 (24.7) |
| Former | 143 (59.1) | 142 (60.4) |
| Active | 49 (20.2) | 33 (14.0) |
| Missing | 0 (0.0) | 2 (0.9) |
| ECOG PS, n (%) | | |
| 0 | 92 (38.0) | 94 (40.0) |
| 1 | 150 (62.0) | 141 (60.0) |
| HPV status, n (%) | | |
| Positive | 53 (21.9) | 50 (21.3) |
| Negative | 189 (78.1) | 185 (78.7) |
| PD-L1 TPS status, n (%) | | |
| TPS < 50% | 176 (72.7) | 173 (73.6) |
| TPS ≥ 50% | 66 (27.3) | 62 (26.4) |
| PD-L1 CPS status, n (%) | | |
| CPS < 20 | 115 (47.5) | 123 (52.3) |
| CPS ≥ 20 | 126 (52.1) | 110 (46.8) |
| Missing | 1 (0.4) | 2 (0.9) |
| Disease status, n (%) | | |
| Metastatic | 173 (71.5) | 154 (65.5) |
| Recurrent | 65 (26.9) | 78 (33.2) |
| Other | 4 (1.7) | 3 (1.3) |
| Presence of brain metastases, n (%) | 3 (1.2) | 1 (0.4) |
| Disease stage, n (%) | | |
| II | 0 (0.0) | 0 (0.0) |
| III | 14 (5.8) | 10 (4.3) |

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study Characteristics Category | Pembrolizumab + chemotherapy[a] N = 242 | Cetuximab + chemotherapy[a] N = 235 |
|---|---|---|
| IVA | 42 (17.4) | 54 (23.0) |
| IVB | 13 (5.4) | 17 (7.2) |
| IVC | 173 (71.5) | 154 (65.5) |
| Location of primary tumour[b], n (%) | | |
| Oral cavity | 77 (31.8) | 73 (31.1) |
| Larynx | 37 (15.3) | 48 (20.4) |
| Hypopharynx | 33 (13.6) | 30 (12.8) |
| Oropharynx | 98 (40.5) | 88 (37.4) |
| Time from prior systemic therapy[c] [months] | | |
| Mean (SD) | 23.2 (29.8)[d] | 28.0 (28.4)[d] |
| Median [Q1; Q3] | 14.5 [10.3; 22.4][d] | 19.7 [11.5; 33.2][d] |
| Time from prior platinum-containing therapy[e] [months] | | |
| Mean (SD) | 24.1 (30.9)[d] | 28.5 (29.0)[d] |
| Median [Q1; Q3] | 14.5 [10.9; 23.4][d] | 18.9 [11.5; 34.2][d] |
| Time from initial diagnosis of the disease [months] | | |
| Mean (SD) | 26.3 (34.5) | 31.6 (37.5) |
| Median [Q1; Q3] | 16.4 (8.1; 27.8) | 20.1 (11.8; 38.5) |
| Treatment discontinuation[f, g], n (%) | 210 (88.6) | 220 (97.3) |
| Study discontinuation[h], n (%) | 13 (5.4)[i] | 14 (6.0) |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. For one patient, several locations were possible.
c. The information is based on 118 (48.8%) patients in the pembrolizumab + chemotherapy arm vs. 118 (50.2%) patients in the cetuximab + chemotherapy arm.
d. Institute's calculation from days into months.
e. The information is based on 109 (45.0) patients in the pembrolizumab + chemotherapy arm vs. 113 (48.1) patients in the cetuximab + chemotherapy arm.
f. At the data cut-off from 25 February 2019, a total of 27 patients in the pembrolizumab arm vs. 0 patients in the comparator arm had already achieved the maximum treatment duration of 24 months. These patients are not counted as treatment discontinuations. At this time point, no patient in the pembrolizumab arm and 6 patients in the comparator arm were receiving ongoing treatment.
b. Data cut-off: 25 February 2019.
h. Without deaths; reasons for discontinuation were: "lost to follow-up" and "withdrawal of consent".
i. Institute's calculation.

5-FU: 5-fluorouracil; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HPV: human papillomavirus; M: male; n: number of patients in the category; N: number of analysed patients in the relevant subpopulation with CPS ≥ 1; PD-L1: programmed cell death ligand 1; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; TPS: Tumour Proportion Score; vs.: versus

The patient characteristics in the relevant subpopulation are largely comparable between the study arms. The mean age of the patients was 61 years, and most of them were male. About 60% of patients had stopped smoking, while on average about 17% were still active smokers.

In each case, just over 2 thirds of the relevant subpopulation had a metastatic and about 30% recurrent disease status. The pembrolizumab + chemotherapy arm included 4 patients and the cetuximab + chemotherapy arm included 3 patients whose disease was neither metastatic nor recurrent and who therefore did not meet the inclusion criteria.

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

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

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Pembrolizumab + chemotherapy[a]**<br>**N = 242** | **Cetuximab + chemotherapy[a]**<br>**N = 235** |
|---|---|---|
| **KEYNOTE-048 (data cut-off 25 February 2019)** | | |
| Treatment duration [months][b] | | |
| Median [Q1; Q3] | 5.78 [2.79; 10.12] | 4.86 [2.33; 7.39] |
| Mean (SD) | 7.72 (7.06) | 6.14 (6.66) |
| Observation period [months] | | |
| Overall survival | | |
| Median [Q1; Q3] | 13.6 [ND] | 10.3 [ND] |
| Mean (SD) | ND | ND |
| Morbidity | ND | ND |
| Health-related quality of life | ND | ND |
| AEs[b, c] | | |
| Median [Q1; Q3] | 6.77 [3.78; 11.11] | 5.85 [3.32; 8.38] |
| Mean (SD) | 8.62 (7.14) | 7.03 (6.60) |
| SAEs[b, c] | | |
| Median [Q1; Q3] | 8.48 [5.13; 12.32] | 7.52 [4.86; 9.99] |
| Mean (SD) | 10.14 (7.46) | 8.46 (6.57) |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Information for the patients who received at least 1 dose of the respective medication: pembrolizumab + chemotherapy N = 237, cetuximab + chemotherapy N = 245, with group allocation according to the medication received.
c. The observation period for side effects is defined as the time from randomization to the occurrence of one of the following events (in each case the first occurring event): 30 days after end of treatment for AEs or 90 days for SAEs, time point of death or time point of data cut-off.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; N: number of analysed patients in the relevant subpopulation with CPS ≥ 1; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

Both the median and the mean treatment duration were sufficiently comparable between both treatment arms. This also applies to the observation periods of the individual outcomes.

***Subsequent therapies***

The KEYNOTE-048 study made no specifications regarding subsequent therapies after discontinuation of the study medication (for example, due to disease progression).

Following treatment with pembrolizumab + chemotherapy, 91 (37.6%) patients in the intervention arm received systemic follow-up therapy as their first subsequent treatment, and 14 (5.8%) patients received radiotherapy as their first subsequent treatment. The respective numbers in the comparator arm were 118 (50.2%) and 15 (6.4%) patients. In both study arms, no patient received a combination of radiotherapy and systemic therapy as first subsequent treatment.

Table 11 shows which systemic therapies patients received after discontinuing the study medication. An overview by combinations or sequence of the subsequent treatments used in the 2 treatment arms is not available.

Table 11: Information on subsequent systemic antineoplastic therapies[a] – RCT, direct comparison: pembrolizumab + chemotherapy[b] vs. cetuximab + chemotherapy[b] (multipage table)

| **Study**<br>**Drug class**<br>**Drug** | **Patients with subsequent therapy n (%)**<br>**Pembrolizumab + chemotherapy[a]**<br>**N = 242** | <br>**Cetuximab + chemotherapy[a]**<br>**N = 235** |
|---|---|---|
| **KEYNOTE-048 (data cut-off 25 February 2019)** | | |
| Patients with ≥ 1 subsequent systemic therapy | 91 (37.6) | 118 (50.2) |
| Chemotherapy | 78 (85.7[c]) | 85 (72.0[c]) |
| Paclitaxel | 41 (45.1[c]) | 39 (33.1[c]) |
| Carboplatin | 22 (24.2[c]) | 22 (18.6[c]) |
| Docetaxel | 14 (15.4[c]) | 28 (23.7[c]) |
| Methotrexate | 18 (19.8[c]) | 11 (9.3[c]) |
| Cisplatin | 12 (13.2[c]) | 12 (10.2[c]) |
| Fluorouracil | 12 (13.2[c]) | 11 (9.3[c]) |
| Gemcitabine | 6 (6.6[c]) | 2 (1.7[c]) |
| Bleomycin | 3 (3.3[c]) | 2 (1.7[c]) |
| Capecitabine | 4 (4.4[c]) | 1 (0.8[c]) |
| Vinorelbine | 3 (3.3[c]) | 2 (1.7[c]) |
| Epirubicin | 2 (2.2[c]) | 0 (0) |
| Gimeracil (+) oteracil (+) tegafur | 2 (2.2[c]) | 0 (0) |
| Mitomycin | 3 (3.3[c]) | 0 (0) |
| Nedaplatin | 2 (2.2[c]) | 0 (0) |
| Tegafur | 2 (2.2[c]) | 1 (0.8[c]) |
| Vincristine | 2 (2.2[c]) | 0 (0) |
| DNA minor groove binders (unspecified) | 1 (1.1[c]) | 0 (0) |
| Cyclophosphamide | 1 (1.1[c]) | 1 (0.8[c]) |
| Gimeracil | 1 (1.1[c]) | 1 (0.8[c]) |
| Tegafur (+) uracil | 1 (1.1[c]) | 0 (0) |
| EGFR inhibitor | 38 (41.8[c]) | 16 (13.6[c]) |
| Cetuximab | 35 (38.5[c]) | 16 (13.6[c]) |
| Panitumumab | 2 (2.2[c]) | 0 (0) |
| Afatinib | 1 (1.1[c]) | 0 (0) |
| EGFR inhibitor antisense oligonucleotide (unspecified) | 1 (1.1[c]) | 0 (0) |
| Immune checkpoint inhibitors | 16 (17.6[c]) | 60 (50.8[c]) |
| Nivolumab | 5 (5.5[c]) | 34 (28.8[c]) |
| Pembrolizumab | 7 (7.7[c]) | 16 (13.6[c]) |
| Durvalumab | 2 (2.2[c]) | 6 (5.1[c]) |
| Tremelimumab | 1 (1.1[c]) | 3 (2.5[c]) |
| Anti-TIGIT monoclonal antibody (unspecified) | 1 (1.1[c]) | 0 (0) |
| Atezolizumab | 1 (1.1[c]) | 1 (0.8[c]) |

Table 11: Information on subsequent systemic antineoplastic therapies[a] – RCT, direct comparison: pembrolizumab + chemotherapy[b] vs. cetuximab + chemotherapy[b] (multipage table)

| **Study** | **Patients with subsequent therapy n (%)** | |
|---|---|---|
| **Drug class**<br>**Drug** | **Pembrolizumab + chemotherapy[a]**<br>**N = 242** | **Cetuximab + chemotherapy[a]**<br>**N = 235** |
| Avelumab | 0 (0) | 1 (0.8[c]) |
| Cemiplimab | 0 (0) | 1 (0.8[c]) |
| Ipilimumab | 0 (0) | 1 (0.8[c]) |
| Kinase inhibitor | 4 (4.4[c]) | 1 (0.8[c]) |
| Palbociclib | 3 (3.3[c]) | 0 (0) |
| ATR serine/threonine kinase inhibitor (unspecified) | 0 (0) | 1 (0.8[c]) |
| Everolimus | 1 (1.1[c]) | 0 (0) |
| Other | 2 (2.2[c]) | 3 (2.5[c]) |
| CXCR2 inhibitor (unspecified) | 1 (1.1[c]) | 1 (0.8[c]) |
| L-006097405 | 1 (1.1[c]) | 1 (0.8[c]) |
| Bevacizumab | 0 (0) | 1 (0.8[c]) |
| Other immunotherapies | 1 (1.1[c]) | 3 (2.5[c]) |
| Anti-ICOS monoclonal antibody (unspecified) | 1 (1.1[c]) | 0 (0) |
| Epacadostat | 0 (0) | 1 (0.8[c]) |
| Talimogene laherparepvec | 0 (0) | 1 (0.8[c]) |
| Utomilumab | 0 (0) | 1 (0.8[c]) |

a. According to the clinical study report, contrary to the information provided by the company in Module 4 B, the information on the specific subsequent systemic therapies apparently refers to all (possibly consecutive) subsequent therapies after the end of treatment with the study medication. It is therefore also unclear whether patients whose first subsequent therapy (second-line therapy) was radiotherapy were also included here.
b. Carboplatin + 5-FU or cisplatin + 5-FU.
c. Institute's calculation, referring to patients with (at least) one disease-related antineoplastic treatment after discontinuation of the study medication.

5-FU: 5-fluorouracil; ATR: ataxia telangiectasia and Rad3 related; CPS: combined positive score; CXCR2: C-X-C motif chemokine receptor 2; DNA: deoxyribonucleic acid; EGFR: epidermal growth factor receptor; ICOS: inducible costimulator molecule; n: number of patients with subsequent therapy; N: number of analysed patients in the relevant subpopulation with CPS ≥ 1; RCT: randomized controlled trial; TIGIT: T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains; vs.: versus

In the KEYNOTE-048 study, about 50% of the adults from the relevant subpopulation received immune checkpoint inhibitor therapy as part of the subsequent therapies (second line and above) following therapy with cetuximab + chemotherapy (see Table 11). Current national and international guidelines primarily recommend programmed cell death 1 (PD-1) inhibitors such as nivolumab or pembrolizumab as subsequent therapies (second line) in the present therapeutic indication, especially in cases of progression during or after platinum-containing therapy [11,12]. It is therefore likely that an immune checkpoint inhibitor would have been indicated as

subsequent therapy for a larger proportion than 50% of the patients. The authors of the publication of the KEYNOTE-048 study also considered it a limitation of the study that availability of PD-1 and PD-L1 inhibitors in the second line setting was inconsistent between the countries [13]. The resulting implications for the present benefit assessment are discussed in Section 2.4.2 and in Section 2.7.4.2 of the full dossier assessment.

**Risk of bias across outcomes (study level)**

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[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-048 | Yes | Yes | No | No | Yes | Yes | Low |

a. Carboplatin + 5-FU or cisplatin + 5-FU.

5-FU: 5-fluorouracil; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the KEYNOTE-048 study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

## 2.4 Results on added benefit

### 2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded with the EORTC QLQ-C30 and QLQ-H&N35 symptom scales
  - health status recorded with the VAS of the EQ-5D questionnaire
- Health-related quality of life

  - recorded with the global health status and the functional scales of the EORTC QLQ-C30 and the functional scales of the EORTC QLQ-H&N35
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related SAEs
  - immune-related severe AEs (CTCAE grade ≥ 3)
  - paronychia (PT, AEs)
  - skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs [CTCAE grade ≥ 3])
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 B) (see Section 2.7.4.3 of the full dossier assessment).

Table 13 shows for which outcomes data were available in the study included.

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

| Study | Outcomes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-H&N35) | SAEs | Severe AEs (CTCAE grade ≥ 3) | Discontinuation due to AEs | Immune-related SAEs and severe AEs (CTCAE grade ≥ 3) | Further specific AEs[b] |
| KEYNOTE-048 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. The following events are considered (MedDRA coding): paronychia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs [CTCAE grade ≥ 3]), anaemia (PT, AEs [CTCAE grade ≥ 3]), stomatitis (PT, AEs [CTCAE grade ≥ 3]), mucosal inflammation (PT, AEs [CTCAE grade ≥ 3]), and respiratory, thoracic and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3]).

5-FU: 5-fluorouracil; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

### 2.4.2 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 + chemotherapy[a] vs. cetuximab + chemotherapy[a]

| Study | Study level | Outcomes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Overall survival | Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-H&N35) | SAEs | Discontinuation due to AEs | Severe AEs (CTCAE grade ≥ 3) | Immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3) | Further specific AEs[b] |
| KEYNOTE-048 | L | H[c] | H[d,e] | H[e, f] | H[d,e] | H[d] | H[e] | H[d] | H[d] | H[d, g] |

a. Carboplatin or cisplatin + 5-FU.
b. The following events are considered (MedDRA coding): paronychia (PT, AEs), skin and subcutaneous tissue disorders (SOC, AEs [CTCAE grade ≥ 3]), anaemia (PT, AEs [CTCAE grade ≥ 3]), stomatitis (PT, AEs [CTCAE grade ≥ 3]), mucosal inflammation (PT, AEs [CTCAE grade ≥ 3]), and respiratory, thoracic and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3]).
c. Not all patients in the comparator arm may have had access to PD-L1 therapies as subsequent therapy (see Section 2.3.2).
d. Incomplete observations for potentially informative reasons.
e. Lack of blinding in subjective recording of outcomes.
f. Large proportion of patients not included in the analysis.
g. Important difference in the median observation period between the intervention arm (6.77 months) and the comparator arm (5.85 months) (applies to PTs).

5-FU: 5-fluorouracil; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PD-L1: programmed cell death ligand 1; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias was rated as high for the results of the outcome "overall survival". The reason for this is that not all patients in the comparator arm of the international study may have had access to PD-L1 therapies as subsequent therapy (see Section 2.3.2 and Section 2.7.4.2 of the full dossier assessment). This deviates from the assessment of the company, which assumed a low risk of bias.

The risk of bias for the results of symptom outcomes recorded with the EORTC QLQ-C30 and QLQ-H&N35 was rated as high due to the lack of blinding in subjective recording of outcomes and due to incomplete observations for potentially informative reasons. This concurs with the company's assessment.

Due to the lack of blinding in subjective recording of outcomes and the high proportion of patients not included in the analysis, the risk of bias was rated as high for the results of the outcome "health status" (EQ-5D VAS). The company used a different operationalization for

this outcome, and therefore did not conduct an assessment of the risk of bias for the results of the operationalization included in the present report.

The risk of bias for the results of health-related quality of life outcomes recorded with the EORTC QLQ-C30 and QLQ-H&N35 was rated as high due to the lack of blinding in subjective recording of outcomes and due to incomplete observations for potentially informative reasons. This concurs with the company's assessment.

The risk of bias was rated as high for the results of the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)", "immune-related SAEs", "immune-related severe AEs (CTCAE grade ≥ 3)" and for the following further specific AEs: paronychia, skin and subcutaneous tissue disorders (CTCAE grade ≥ 3), anaemia (CTCAE grade ≥ 3), stomatitis (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), and respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3). The reason for this is in each case the incomplete observation for potentially informative reasons. Furthermore, there were no survival time analyses for PTs, and the different observation periods therefore resulted in an additional high risk of bias in the analyses used for PTs (based on the number of patients with at least one event).

For the results on the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)", "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)", the assessment of the risk of bias deviates from that of the company, which assumed a low risk of bias in each case. Regarding the results on the further specific AEs, the company did not conduct an assessment of the risk of bias per specific AE. For AEs recorded using SOCs, the company generally assumed a low risk of bias of the results, however.

For the results of the outcome "discontinuation due to AEs", the risk of bias was rated as high due to lack of blinding in subjective recording of outcomes. This deviates from the assessment of the company, which assumed a low risk of bias.

Further information on the risk of bias can be found in Section 2.7.4.2 of the full dossier assessment.

### 2.4.3 Results

Table 15 and Table 16 summarize the results on the comparison of pembrolizumab + chemotherapy with cetuximab + chemotherapy in patients with metastatic or unresectable recurrent HNSCC whose tumours express PD-L1 with a CPS ≥ 1. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

If presented by the company in the dossier, Kaplan-Meier curves for usable event time analyses can be found in Appendix A of the full dossier assessment. Results on common AEs are presented in Appendix B of the full dossier assessment. Appendix E of the full dossier assessment additionally presents the results on common immune-related AEs and on common

immune-related severe AEs (CTCAE grade ≥ 3) for the total population; there are no respective data for the relevant subpopulation.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study<br>Outcome category<br>Outcome | Pembrolizumab + chemotherapy[a] | | Cetuximab + chemotherapy[a] | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] |
|---|---|---|---|---|---|
| | 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][b]; p-value[c] |
| **KEYNOTE-048 (data cut-off 25 February 2019)** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 242 | 13.6 [10.7; 15.5]<br>177 (73.1) | 235 | 10.4 [9.1; 11.7]<br>213 (90.6) | 0.65 [0.53; 0.80];<br>< 0.001 |
| **Morbidity** | | | | | |
| Symptoms (EORTC QLQ-C30 symptom scales)[d] | | | | | |
| Fatigue | 231 | 7.5 [4.0; NC]<br>93 (40.3) | 220 | 7.9 [4.5; NC]<br>85 (38.6) | 1.07 [0.79; 1.44];<br>0.677 |
| Nausea and vomiting | 231 | NA [12.4; NC]<br>67 (29.0) | 220 | NA<br>54 (24.5) | 1.18 [0.83; 1.70];<br>0.359 |
| Pain | 231 | NA [10.6; NC]<br>61 (26.4) | 220 | NA<br>44 (20.0) | 1.36 [0.92; 2.02];<br>0.125 |
| Dyspnoea | 231 | NA<br>54 (23.4) | 220 | NA<br>33 (15.0) | 1.55 [1.00; 2.40];<br>0.051 |
| Insomnia | 231 | NA<br>48 (20.8) | 220 | NA<br>28 (12.7) | 1.65 [1.03; 2.65];<br>0.036 |
| Appetite loss | 231 | NA [12.2; NC]<br>64 (27.7) | 220 | NA [10.6; NC]<br>56 (25.5) | 1.11 [0.77; 1.60];<br>0.564 |
| Constipation | 231 | NA [10.6; NC]<br>63 (27.3) | 220 | NA<br>46 (20.9) | 1.21 [0.82; 1.77];<br>0.340 |
| Diarrhoea | 231 | NA<br>26 (11.3) | 220 | NA<br>33 (15.0) | 0.66 [0.40; 1.12];<br>0.125 |
| Symptoms (EORTC QLQ-H&N35 symptom scales)[d] | | | | | |
| Pain[e] | 230 | NA<br>57 (24.8) | 220 | NA<br>39 (17.7) | 1.43 [0.95; 2.16];<br>0.088 |
| Problems with swallowing[f] | 230 | NA<br>45 (19.6) | 220 | NA [10.6; NC]<br>42 (19.1) | 0.94 [0.61; 1.45];<br>0.791 |
| Problems with senses | 230 | NA [9.9; NC]<br>73 (31.7) | 220 | NA<br>60 (27.3) | 1.14 [0.81; 1.61];<br>0.455 |
| Problems with speech | 230 | NA<br>57 (24.8) | 220 | NA<br>56 (25.5) | 0.92 [0.63; 1.34];<br>0.663 |
| Problems with teeth | 230 | NA [23.7; NC]<br>35 (15.2) | 220 | NA<br>35 (15.9) | 0.83 [0.51; 1.34];<br>0.444 |

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study<br>Outcome category<br>Outcome | Pembrolizumab + chemotherapy[a] | | Cetuximab + chemotherapy[a] | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] |
|---|---|---|---|---|---|
| | 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][b]; p-value[c] |
| Problems with mouth opening | 230 | NA<br>38 (16.5) | 220 | NA<br>41 (18.6) | 0.80 [0.51; 1.26]; 0.337 |
| Dry mouth | 230 | NA<br>45 (19.6) | 220 | NA<br>52 (23.6) | 0.75 [0.50; 1.12]; 0.163 |
| Sticky saliva | 230 | NA<br>50 (21.7) | 220 | NA<br>45 (20.5) | 1.10 [0.73; 1.65]; 0.659 |
| Cough | 230 | NA<br>41 (17.8) | 220 | NA<br>40 (18.2) | 0.91 [0.59; 1.42]; 0.685 |
| Feeling ill | 230 | NA<br>48 (20.9) | 220 | NA<br>36 (16.4) | 1.22 [0.79; 1.89]; 0.372 |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30 (functional scales and global health status scale)[g] | | | | | |
| Global health status[h] | 231 | NA<br>62 (26.8) | 220 | 13.4 [13.4; NC]<br>46 (20.9) | 1.31 [0.89; 1.93]; 0.168 |
| Physical functioning | 231 | NA [6.9; NC]<br>79 (34.2) | 220 | NA [10.9; NC]<br>61 (27.7) | 1.28 [0.91; 1.79]; 0.156 |
| Role functioning | 231 | NA<br>75 (32.5) | 220 | NA [4.9; NC]<br>79 (35.9) | 0.92 [0.66; 1.26]; 0.590 |
| Emotional functioning | 231 | NA<br>36 (15.6) | 220 | NA<br>32 (14.5) | 1.03 [0.63; 1.66]; 0.913 |
| Cognitive functioning | 231 | NA [23.7; NC]<br>65 (28.1) | 220 | NA [10.6; NC]<br>55 (25.0) | 1.06 [0.73; 1.53]; 0.762 |
| Social functioning | 231 | NA [12.2; NC]<br>62 (26.8) | 220 | NA [6.5; NC]<br>72 (32.7) | 0.77 [0.55; 1.09]; 0.141 |
| EORTC QLQ-H&N35 (functional scales)[d] | | | | | |
| Problems with social eating | 230 | NA [12.9; NC]<br>55 (23.9) | 220 | NA<br>41 (18.6) | 1.19 [0.79; 1.79]; 0.416 |
| Problems with social contact | 230 | NA<br>46 (20.0) | 220 | NA [10.9; NC]<br>49 (22.3) | 0.82 [0.54; 1.23]; 0.334 |
| Reduced sexuality | 229 | NA<br>65 (28.4) | 220 | NA [9.1; NC]<br>67 (30.5) | 0.86 [0.61 1.22]; 0.404 |

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study<br>Outcome category<br>Outcome | Pembrolizumab + chemotherapy[a] | | Cetuximab + chemotherapy[a] | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] |
|---|---|---|---|---|---|
| | 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][b]; p-value[c] |
| **Side effects** | | | | | |
| *AEs (supplementary information)* | *237* | *0.1 [0.1; 0.1][i]*<br>*233 (98.3)* | *245* | *0.1 [0.1; 0.1][i]*<br>*244 (99.6)* | – |
| SAEs | 237 | 3.1 [2.4; 4.4][i]<br>150 (63.3) | 245 | 10.6 [5.1; NC][i]<br>121 (49.4) | 1.39 [1.09; 1.77][j]; 0.007 |
| Severe AEs (CTCAE grade ≥ 3) | 237 | 1.1 [0.7; 1.4][i]<br>203 (85.7) | 245 | 0.9 [0.7; 1.2][i]<br>203 (82.9) | 1.03 [0.85; 1.26][j]; 0.744 |
| Discontinuation due to AEs | 237 | NA [12.6; NC][i]<br>82 (34.6) | 245 | 39.3 [39.3; NC][i]<br>67 (27.3) | 1.24 [0.90; 1.71][j]; 0.196 |
| Immune-related AEs (supplementary information)[k] | *237* | *NA [22.2; NC][i]*<br>*63 (26.6)* | *245* | *NA*<br>*59 (24.1)* | – |
| Immune-related SAEs | 237 | NA<br>12 (5.1) | 245 | NA<br>10 (4.1) | 1.20 [0.52; 2.78][j]; 0.671 |
| Immune-related severe AEs (CTCAE grade ≥ 3) | 237 | NA<br>14 (5.9) | 245 | NA<br>27 (11.0) | 0.44 [0.23; 0.86][j]; 0.015 |
| Paronychia (PT, AEs) | 237 | ND<br>0 (0) | 245 | ND<br>30 (12.2) | RR: 0.02 [0.00; 0.28]; < 0.001[l] |
| Skin and subcutaneous tissue disorders (SOC, AEs [CTCAE grade ≥ 3]) | 237 | NA<br>7 (3.0) | 245 | NA<br>24 (9.8) | 0.26 [0.11; 0.61][j]; 0.002 |
| Anaemia (PT, AEs [CTCAE grade ≥ 3]) | 237 | ND<br>57 (24.1) | 245 | ND<br>36 (14.7) | RR: 1.64 [1.12; 2.39][l]; 0.010 |
| Stomatitis (PT, AEs [CTCAE grade ≥ 3]) | 237 | ND<br>20 (8.4) | 245 | ND<br>9 (3.7) | RR: 2.30 [1.07; 4.94]; 0.028[l] |
| Mucosal inflammation (PT, AEs [CTCAE grade ≥ 3]) | 237 | ND<br>25 (10.5) | 245 | ND<br>13 (5.3) | RR: 1.99 [1.04; 3.79]; 0.034[l] |
| Respiratory, thoracic and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3]) | 237 | NA<br>35 (14.8) | 245 | NA<br>18 (7.3) | 1.91 [1.08; 3.38][j]; 0.027 |

Table 15: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study<br>Outcome category<br>Outcome | Pembrolizumab + chemotherapy[a] | | Cetuximab + chemotherapy[a] | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] |
|---|---|---|---|---|---|
| | 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][b]; p-value[c] |

a. Carboplatin or cisplatin + 5-FU.
b. Unless stated otherwise: Cox proportional hazards model stratified by ECOG PS, HPV status and PD-L1 status. If the number of events in a stratum is < 5, the stratification factors are cancelled successively (ECOG PS → HPV status → PD-L1 status) until the number of events in each stratum is ≥ 5.
c. p-value: Wald test.
d. Time to first confirmed clinically relevant deterioration, defined as an increase in score by at least 10 points from baseline, confirmed at the next recording.
e. Discrepant information in the CSR: patients with event: 49 (21.3) vs. 37 (16.8); HR = 1.30 [0.84; 2.00]; p = 0.885 (one-sided).
f. Discrepant information in the CSR: patients with event: 39 (17.0) vs. 36 (16.4); HR = 0.94 [0.59; 1.50]; p = 0.402 (one-sided).
g. Time to first confirmed clinically relevant deterioration, defined as a decrease in score by at least 10 points from baseline, confirmed at the next recording.
h. Discrepant information in the CSR: patients with event: 55 (23.8) vs. 36 (16.4); HR = 1.50 [0.98; 2.29]; p = 0.970 (one-sided).
i. Institute's calculation from weeks into months.
j. HR and 95% CI: Cox proportional hazards model.
k. See Section 2.7.4.3.2 of the full dossier assessment for reasons.
l. Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [14]).

5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CPS: combined positive score; CSR: clinical study report; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HPV: human papillomavirus; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients in the relevant subpopulation with CPS ≥ 1; NA: not achieved; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 16: Results (morbidity, continuous) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a]

| Study<br>Outcome category<br>Outcome | Pembrolizumab + chemotherapy[a] | | | Cetuximab + chemotherapy[a] | | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] |
|---|---|---|---|---|---|---|---|
| | N[b] | Value at baseline mean (SD) | Value at week 9 mean (SD) | N[b] | Value at baseline mean (SD) | Value at week 9 mean (SD) | MD [95% CI][c]; p-value |
| **KEYNOTE-048** | | | | | | | |
| **Morbidity** | | | | | | | |
| Health status (EQ-5D VAS)[d] | 182 | 68 (19.6) | 72.9 (16.9) | 170 | 67.1 (19.6) | 72.9 (15.9) | 0.20 [−3.30; 3.70]; 0.910 |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
c. Effect, CI and p-value: Institute's calculation (t-test).
d. Higher values indicate better health status; positive effects indicate an advantage for the intervention.

5-FU: 5-fluorouracil; CI: confidence interval; CPS: combined positive score; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; N: number of analysed patients in the relevant subpopulation with CPS ≥ 1; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Based on the available data, no more than hints, e.g. of an added benefit, can generally be determined for all outcomes. Due to the size of the effect, the outcome-specific certainty of the results may not be downgraded (for reasons, see result description below and Section 2.7.4.2 of the full dossier assessment).

## Mortality

### *Overall survival*

A statistically significant difference in favour of pembrolizumab was shown for the outcome "overall survival". This resulted in a hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT.

This deviates from the assessment of the company, which saw an indication of an added benefit of pembrolizumab in comparison with cetuximab + chemotherapy for the outcome "overall survival".

## Morbidity

### *Symptoms (EORTC QLQ-C30)*

*Fatigue*

No statistically significant difference between the treatment groups was shown for the outcome "fatigue". There was an effect modification for the characteristic "sex", however (see Section 2.4.4). For men, the effect modification resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not

proven for this patient group. For women, this resulted in a hint of lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT.

This deviates from the assessment of the company, which derived no hint of a lesser or added benefit of pembrolizumab in comparison with the ACT for the outcome "fatigue". The company did not use the results on the subgroup analyses for the derivation of an added benefit.

*Insomnia*

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus the ACT was shown for the outcome "insomnia". The effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

This concurs with the company's assessment.

*Nausea and vomiting, pain, dyspnoea, appetite loss, constipation and diarrhoea*

There were no statistically significant differences between the treatment groups for each of the following outcomes: nausea and vomiting, pain, dyspnoea, appetite loss, constipation, and diarrhoea. In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

This concurs with the company's assessment.

***Symptoms (EORTC QLQ-H&N35)***

*Pain*

No statistically significant difference between the treatment groups was shown for the outcome "pain". There was an effect modification for the characteristic "disease status", however (see Section 2.4.4). The effect modification resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients with metastatic disease. A statistically significant difference in favour of pembrolizumab + chemotherapy versus the ACT was shown for patients with (unresectable) recurrent disease. The effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT for this patient group; an added benefit is therefore not proven for this patient group.

This concurs with the company's assessment.

*Dry mouth*

No statistically significant difference between the treatment groups was shown for the outcome "dry mouth". There was an effect modification for the characteristic "smoking status", however

(see Section 2.4.4). A statistically significant difference in favour of pembrolizumab + chemotherapy versus the ACT was shown for patients who were former or never smokers. The effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT for this patient group; an added benefit is therefore not proven for this patient group. For patients who are active smokers, there was also no hint of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

This concurs with the company's assessment.

*Feeling ill*

No statistically significant difference between the treatment groups was shown for the outcome "feeling ill". There was an effect modification for the characteristic "sex", however (see Section 2.4.4). For men, the effect modification resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group. For women, this resulted in a hint of lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT.

This deviates from the assessment of the company, which derived no hint of a lesser or added benefit of pembrolizumab in comparison with the ACT for the outcome "feeling ill". The company did not use the results on the subgroup analyses for the derivation of an added benefit.

*Problems with swallowing, senses, speech, teeth, mouth opening, sticky saliva and coughing*

No statistically significant differences between the treatment groups were shown for any of the following outcomes: problems with swallowing, senses, speech, teeth, mouth opening, sticky saliva and coughing. In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

This concurs with the company's assessment.

***Health status (EQ-5D VAS)***

The outcome "health status" was recorded with the EQ-5D VAS. In the present benefit assessment, the analysis was conducted as change at week 9 from baseline (see Section 2.7.4.3.2 of the full dossier assessment). There was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as it also considered an added benefit for this outcome as not proven; however, it used the analyses on the time to first confirmed deterioration by ≥ 7 or ≥ 10 points for this purpose.

**Health-related quality of life**

***EORTC QLQ-C30 (functional scales and global health status scale)***

*Physical functioning*

There was no statistically significant difference between the treatment groups for the outcome "physical functioning". There was an effect modification for the characteristic "age", however (see Section 2.4.4). The effect modification resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients under the age of 65 years. For patients aged 65 years or older, there was no hint of lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

This deviates from the assessment of the company, which derived no hint of a lesser or added benefit of pembrolizumab in comparison with the ACT for the outcome "physical functioning". The company did not use the results on the subgroup analyses for the derivation of an added benefit.

*Cognitive functioning*

There was no statistically significant difference between the treatment groups for the outcome "cognitive functioning". There was an effect modification for the characteristic "sex", however (see Section 2.4.4). For men, the effect modification resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group. For women, this resulted in a hint of lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT.

This deviates from the assessment of the company, which derived no hint of a lesser or added benefit of pembrolizumab in comparison with the ACT for the outcome "cognitive functioning". The company did not use the results on the subgroup analyses for the derivation of an added benefit.

*Global health status, role functioning, emotional functioning and social functioning*

No statistically significant differences between the treatment groups were shown for the outcomes "global health status", "role functioning", "emotional functioning" and "social functioning". In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

This concurs with the company's assessment.

***EORTC QLQ-H&N35 (functional scales)***

*Problems with social eating*

No statistically significant difference between the treatment groups was shown for the outcome "problems with social eating". There was an effect modification for the characteristic "age",

however (see Section 2.4.4). The effect modification resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients under the age of 65 years. For patients aged 65 years or older, there was no hint of lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

This deviates from the assessment of the company, which derived no hint of a lesser or added benefit of pembrolizumab in comparison with the ACT for the outcome "problems with social eating". The company did not use the results on the subgroup analyses for the derivation of an added benefit. Furthermore, the company allocated the entire EORTC QLQ-H&N35 questionnaire to the outcome category of morbidity.

*Problems with social contact and reduced sexuality*

No statistically significant differences between the treatment groups were shown for the outcomes "problems with social contact" and "reduced sexuality". In each case, this resulted in no hint of a lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for these outcomes.

This concurs with the assessment of the company insofar as it also derived no hint of lesser or added benefit for the outcomes "problems with social contact" and "reduced sexuality". Deviating from the present benefit assessment, the company allocated the entire EORTC QLQ-H&N35 questionnaire to the outcome category of morbidity.

**Side effects**

In the outcome category of side effects, it is not described to what extent the conclusions on the added benefit made here deviates from the assessment of the company for the following outcomes. This is justified below:

The company derived no indication of greater or lesser benefit for the entire outcome category of side effects. However, it did not make any statements on the probability and extent of any possibly existing greater or lesser harm at the level of individual outcomes. With the exception of the immune-related severe AEs (CTCAE grade ≥ 3), the company did not use any outcomes on specific AEs for the derivation of an added benefit.

***Serious adverse events***

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy was shown for the outcome "SAEs". This resulted in a hint of greater harm from pembrolizumab + chemotherapy in comparison with the ACT.

***Severe adverse events (CTCAE grade ≥ 3)***

No statistically significant difference between the treatment groups was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in no hint of greater or lesser harm of pembrolizumab + chemotherapy versus the ACT; greater or lesser harm is therefore not proven.

***Discontinuation due to adverse events***

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of pembrolizumab + chemotherapy versus the ACT; greater or lesser harm is therefore not proven.

***Specific adverse events***

*Immune-related serious adverse events*

No statistically significant difference between the treatment groups was shown for the outcome "immune-related SAEs". This resulted in no hint of greater or lesser harm of pembrolizumab + chemotherapy versus the ACT; greater or lesser harm is therefore not proven.

*Immune-related severe adverse events (CTCAE grade ≥ 3)*

A statistically significant difference in favour of pembrolizumab + chemotherapy was shown for the outcome "immune-related severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab + chemotherapy in comparison with the ACT.

*Paronychia*

A statistically significant difference in favour of pembrolizumab + chemotherapy was shown for the outcome "paronychia". Despite the high risk of bias, the certainty of results was not downgraded in this outcome (see Section 2.7.4.2 of the full dossier assessment). This resulted in an indication of lesser harm from pembrolizumab + chemotherapy in comparison with the ACT.

*Skin and subcutaneous tissue disorders (CTCAE grade ≥ 3)*

A statistically significant difference in favour of pembrolizumab + chemotherapy was shown for the outcome "skin and subcutaneous tissue disorders (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab + chemotherapy in comparison with the ACT.

*Anaemia (CTCAE grade ≥ 3), stomatitis (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3) and respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)*

Statistically significant differences to the disadvantage of pembrolizumab + chemotherapy in comparison with cetuximab + chemotherapy were shown for the following outcomes: anaemia (CTCAE grade ≥ 3), stomatitis (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3) and respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3). In each case, this resulted in a hint of greater harm from pembrolizumab + chemotherapy in comparison with the ACT.

### 2.4.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered for the present benefit assessment:

- sex (male/female)
- age (< 65 years/≥ 65 years)

- PD-L1 status (CPS < 20/CPS ≥ 20)
- PD-L1 status (TPS < 50%/TPS ≥ 50%)
- region (North America/Europe/rest of the world)
- smoking status (never/former/active)
- disease status (metastatic/recurrent)

Interaction tests were performed if at least 10 patients per subgroup were included in the analysis. For binary data, 10 events had to have occurred in at least 1 subgroup.

Only 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the chosen specific AEs, no analyses on subgroup analyses were available, except for immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3).

The company did not use the results on the subgroup analyses for any of the outcomes for the derivation of an added benefit.

Table 17 presents the relevant results for subgroups.

Table 17: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study<br>Outcome<br>Characteristic<br>Subgroup | Pembrolizumab + chemotherapy[a] | | Cetuximab + chemotherapy[a] | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] | |
|---|---|---|---|---|---|---|
| | 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][b] | p-value[c] |
| **KEYNOTE-048 (data cut-off 25 February 2019)** | | | | | | |
| **Morbidity** | | | | | | |
| Symptoms (EORTC QLQ-C30 symptom scales)[d] | | | | | | |
| Fatigue | | | | | | |
| Sex | | | | | | |
| Male | 179 | 10.6 [5.1; NC]<br>69 (38.5) | 190 | 7.5 [3.6; NC]<br>77 (40.5) | 0.93 [0.67; 1.29] | 0.658 |
| Female | 52 | 2.4 [1.0; NC]<br>24 (46.2) | 30 | 7.9 [5.3; NC]<br>8 (26.7) | 2.80 [1.16; 6.75] | 0.022 |
| Total | | | | | Interaction: | 0.021[e] |
| Symptoms (QLQ-H&N35 symptom scales)[d] | | | | | | |
| Pain | | | | | | |
| Disease status | | | | | | |
| Metastatic | 163 | NA [9.3; NC]<br>50 (30.7) | 143 | NA<br>26 (18.2) | 1.91 [1.18; 3.08] | 0.009 |
| Recurrent | 63 | NA<br>6 (9.5) | 74 | NA [9.8; NC]<br>13 (17.6) | 0.27 [0.08; 0.95] | 0.042 |
| Total | | | | | Interaction: | 0.005[e] |
| *Dry mouth (supplementary information)* | | | | | | |
| *Smoking status* | | | | | | |
| *Never* | *44* | *NA [7.9; NC]*<br>*11 (25.0)* | *56* | *NA*<br>*12 (21.4)* | *1.03 [0.43; 2.45]* | *0.950* |
| *Former* | *137* | *NA*<br>*17 (12.4)* | *132* | *NA [7.8; NC]*<br>*32 (24.2)* | *0.41 [0.22; 0.76]* | *0.005* |
| *Active* | *49* | *NA [3.4; NC]*<br>*17 (34.7)* | *31* | *NA [5.0; NC]*<br>*8 (25.8)* | *1.84 [0.79; 4.31]* | *0.159* |
| *Total* | | | | | *Interaction:* | *0.014[e]* |
| Dry mouth | | | | | | |
| Smoking status | | | | | | |
| Never or former[f] | 181[g] | ND<br>28 (15.5)[g] | 188[g] | ND<br>44 (23.4)[g] | 0.56 [0.34; 0.93] | 0.024 |
| Active | 49 | NA [3.4; NC]<br>17 (34.7) | 31 | NA [5.0; NC]<br>8 (25.8) | 1.84 [0.79; 4.31] | 0.159 |
| Total | | | | | Interaction: | 0.018[f] |

Table 17: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study<br>Outcome<br>Characteristic<br>Subgroup | Pembrolizumab + chemotherapy[a] | | Cetuximab + chemotherapy[a] | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] | |
|---|---|---|---|---|---|---|
| | 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][b] | p-value[c] |
| Feeling ill | | | | | | |
| Sex | | | | | | |
| Male | 178 | NA<br>31 (17.4) | 190 | NA 33 (17.4) | 0.91 [0.55; 1.50] | 0.717 |
| Female | 52 | NA [2.4; NC]<br>17 (32.7) | 30 | NA<br>3 (10.0) | 5.35 [1.52; 18.79] | 0.009 |
| Total | | | | | Interaction: | 0.010[e] |
| **Health-related quality of life** | | | | | | |
| EORTC QLQ-C30 (functional scales)[h] | | | | | | |
| Physical functioning | | | | | | |
| Age | | | | | | |
| < 65 years | 144 | NA [6.2; NC]<br>49 (34.0) | 139 | NA<br>30 (21.6) | 1.75 [1.10; 2.77] | 0.018 |
| ≥ 65 years | 87 | NA [4.1; NC]<br>30 (34.5) | 81 | 6.5 [3.9; NC]<br>31 (38.3) | 0.72 [0.42; 1.24] | 0.234 |
| Total | | | | | Interaction: | 0.014[e] |
| Cognitive functioning | | | | | | |
| Sex | | | | | | |
| Male | 179 | NA [23.7; NC]<br>44 (24.6) | 190 | NA [10.6; NC]<br>50 (26.3) | 0.84 [0.55; 1.27] | 0.412 |
| Female | 52 | 4.9 [2.1; NC]<br>21 (40.4) | 30 | NA [7.9; NC]<br>5 (16.7) | 4.20 [1.39; 12.67] | 0.011 |
| Total | | | | | Interaction: | 0.008[e] |
| EORTC QLQ-H&N35 (functional scales)[d] | | | | | | |
| Problems with social eating | | | | | | |
| Age | | | | | | |
| < 65 years | 144 | NA [10.0; NC]<br>38 (26.4) | 139 | NA<br>22 (15.8) | 1.78 [1.04; 3.05] | 0.036 |
| ≥ 65 years | 86 | NA [12.9; NC]<br>17 (19.8) | 81 | NA [7.6; NC]<br>19 (23.5) | 0.54 [0.26; 1.12] | 0.099 |
| Total | | | | | Interaction: | 0.010[e] |

Table 17: Subgroups (morbidity, health-related quality of life) – RCT, direct comparison: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| Study<br>Outcome<br>Characteristic<br>Subgroup | Pembrolizumab + chemotherapy[a] | | Cetuximab + chemotherapy[a] | | Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] | |
|---|---|---|---|---|---|---|
| | 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][b] | p-value[c] |

a. Carboplatin or cisplatin + 5-FU.
b. Cox proportional hazards model stratified by ECOG PS, HPV status and PD-L1 status.
c. Unless stated otherwise: Wald test.
d. Time to first confirmed clinically relevant deterioration, defined as an increase in score by at least 10 points from baseline, confirmed at the next recording.
e. Q test.
f. Institute's calculation: meta-analytical summary of the subgroup results for smoking status never and former (fixed-effect model).
g. Institute's calculation.
h. Time to first confirmed clinically relevant deterioration, defined as a decrease in score by at least 10 points from baseline, confirmed at the next recording.

5-FU: 5-fluorouracil; CI: confidence interval; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EORTC: European Organisation for Research and Treatment of Cancer; HPV: human papillomavirus; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients in the relevant subpopulation with CPS ≥ 1; NA: not achieved; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; vs.: versus

## Morbidity

### *Symptoms (EORTC QLQ-C30 symptom scales)*

*Fatigue*

There was an effect modification by the characteristic "sex" for the outcome "fatigue".

For men, there was no statistically significant difference for the outcome "fatigue". For women, there was a statistically significant difference to the disadvantage of the intervention for the outcome "fatigue". This resulted in a hint of lesser benefit from pembrolizumab + chemotherapy in comparison with the ACT for women. For men, there was no hint of an added benefit or lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit for this patient group is therefore not proven.

### *Symptoms (EORTC QLQ-H&N35 symptom scales)*

*Pain*

A statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus the ACT was shown for patients with metastatic disease status. For patients with

recurrent disease status, a statistically significant difference in favour of the intervention was shown for the outcome "pain". The effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients with metastatic disease status. For patients with recurrent disease status, there was no hint of lesser benefit or of an added benefit of pembrolizumab + chemotherapy versus the ACT; an added benefit is therefore not proven for this patient group.

*Dry mouth*

For the symptom of dry mouth, there was an effect modification (interaction test: $p = 0.014$) by the characteristic "smoking status" with the subgroups never, former and active. In the present data situation, the subgroups with homogeneous effects (smoking status never and former) were aggregated with a fixed-effect model due to the identical study (see Figure 10 in Section D.1 of the full dossier assessment). The interaction test between the subgroup results from the characteristic "smoking status" (aggregated subgroup of never and former versus active) resulted in a p-value of 0.018.

For patients who were former or never smokers, a statistically significant difference in favour of pembrolizumab + chemotherapy versus the ACT was shown for the outcome "dry mouth". The effect in this non-serious/non-severe symptom was no more than marginal, however. For patients who were active smokers, there was no statistically significant difference in the outcome "dry mouth". Hence, both for patients who were former or never smokers, and for patients who were active smokers, there was no hint of an added benefit or lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit is therefore not proven for this patient group.

*Sticky saliva*

An effect modification by the characteristic "PD-L1 status" recorded using TPS was shown for the outcome "sticky saliva". This was not reflected in the results on the second investigated characteristic on PD-L1 status (CPS < 20 versus CPS ≥ 20), however, for which no effect modification was shown.

It is unclear in the present therapeutic indication whether TPS or CPS is the characteristic to be preferred and to what extent the respective cut-off values of the 2 investigated characteristics TPS and CPS correlate with each other. Since the investigations of the PD-L1 status according to TPS or CPS yielded different results regarding the effect modification, the effect modification observed for the characteristic of TPS was not considered further. The results of the subgroup analyses on PD-L1 status according to TPS and CPS are presented in Section D.2 of the full dossier assessment for clarification.

*Feeling ill*

For men, there was no statistically significant difference for the outcome "feeling ill". For women, there was a statistically significant difference to the disadvantage of the intervention

for the outcome "feeling ill". This resulted in a hint of lesser benefit from pembrolizumab + chemotherapy in comparison with the ACT for women. For men, there was no hint of an added benefit or lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit for this patient group is therefore not proven.

***Health-related quality of life (EORTC QLQ-C30 functional scales)***

*Physical functioning*

For the outcome "physical functioning", a statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus the ACT was shown for patients under the age of 65 years. No statistically significant difference for the outcome "physical functioning" was shown for patients aged 65 years or older. This resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients under the age of 65 years. For patients aged 65 years or older, there was no hint of an added benefit or lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit for this patient group is therefore not proven.

*Cognitive functioning*

For men, there was no statistically significant difference for the outcome "cognitive functioning". For women, a statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus the ACT was shown for the outcome "cognitive functioning". This resulted in a hint of lesser benefit from pembrolizumab + chemotherapy in comparison with the ACT for women. For men, there was no hint of an added benefit or lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit for this patient group is therefore not proven.

***Health-related quality of life (EORTC QLQ-H&N35 functional scales)***

*Problems with social eating*

For the outcome "problems with social eating", a statistically significant difference to the disadvantage of pembrolizumab + chemotherapy versus the ACT was shown for patients under the age of 65 years. No statistically significant difference for the outcome "problems with social eating" was shown for patients aged 65 years or older. This resulted in a hint of lesser benefit of pembrolizumab + chemotherapy versus the ACT for patients under the age of 65 years. For patients aged 65 years or older, there was no hint of an added benefit or lesser benefit of pembrolizumab + chemotherapy in comparison with the ACT; an added benefit for this patient group is therefore not proven.

**Immune-related severe adverse events (CTCAE grade ≥ 3)**

There was an effect modification by the characteristic "PD-L1 status" recorded using TPS. This was not reflected in the results on the second investigated characteristic on PD-L1 status (CPS < 20 versus CPS ≥ 20), however, for which no effect modification was shown.

It is unclear in the present therapeutic indication whether TPS or CPS is the characteristic to be preferred and to what extent the respective cut-off values correlate with each other. Since the investigations of the PD-L1 status according to TPS or CPS yielded different results regarding the effect modification, the effect modification observed for the characteristic of TPS was not considered further. The results of the subgroup analyses on PD-L1 status according to TPS and CPS are presented in Section D.2 of the full dossier assessment for clarification.

## 2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [2].

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.

### 2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 18).

**Determination of the outcome category for the outcomes on symptoms and side effects**

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

***EORTC QLQ-C30 (symptom scales): fatigue***

The dossier did not contain any information on the assignment of the severity category for the outcome “fatigue” of the EORTC QLQ-C30 (symptom scales). Therefore, the outcome “fatigue” was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

The company did not assign these outcomes to an outcome category.

***EORTC QLQ-H&N35 (symptom scales): dry mouth, pain and feeling ill***

There was no information available in the dossier that would allow assigning the severity category for the outcomes “dry mouth”, “pain” and “feeling ill” of the EORTC QLQ-H&N35 (symptom scales). Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms/late complications.

The company did not assign these outcomes to an outcome category.

***Further specific adverse events***

For the specific AE "paronychia", there was no information available to draw conclusions on the proportions of SAEs or severe AEs (CTCAE grade ≥ 3) in this outcome. Therefore, the outcome was assigned to the outcome category of non-serious/non-severe AEs.

By definition, only severe AEs (CTCAE grade ≥ 3) are included in the following outcomes: skin and subcutaneous tissue disorders (CTCAE grade ≥ 3), anaemia (CTCAE grade ≥ 3), stomatitis (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), and respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3). For this reason, these outcomes were assigned to the outcome category of serious/severe AEs.

The company did not assign the outcomes mentioned to an outcome category.

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| **Outcome category**<br>**Outcome** | **Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a]**<br>**Quantile of the time to event (months) or MD**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| **Mortality** | | |
| Overall survival | Median: 13.6 vs. 10.4<br>HR: 0.65 [0.53; 0.80];<br>p < 0.001<br>probability: "hint" | Outcome category: mortality<br>$CI_u < 0.85$<br>added benefit, extent: "major" |
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30) | | |
| Fatigue<br>Sex<br>Male | Median: 10.6 vs. 7.5<br>HR: 0.93 [0.67; 1.29];<br>p = 0.658 | Lesser benefit/added benefit not proven |
| Female | Median: 2.4 vs. 7.9<br>HR: 2.80 [1.16; 6.75];<br>HR[d]: 0.36 [0.15; 0.86];<br>p = 0.022<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>lesser benefit, extent: "minor" |
| Nausea and vomiting | Median: NA vs. NA<br>HR: 1.18 [0.83; 1.70];<br>p = 0.359 | Lesser benefit/added benefit not proven |
| Pain | Median: NA vs. NA<br>HR: 1.36 [0.92; 2.02];<br>p = 0.125 | Lesser benefit/added benefit not proven |
| Dyspnoea | Median: NA vs. NA<br>HR: 1.55 [1.00; 2.40];<br>p = 0.051 | Lesser benefit/added benefit not proven |
| Insomnia | Median: NA vs. NA<br>HR: 1.65 [1.03; 2.65];<br>HR[d]: 0.61 [0.38; 0.97];<br>p = 0.036 | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>lesser benefit/added benefit not proven[e] |
| Appetite loss | Median: NA vs. NA<br>HR: 1.11 [0.77; 1.60];<br>p = 0.564 | Lesser benefit/added benefit not proven |
| Constipation | Median: NA vs. NA<br>HR: 1.21 [0.82; 1.77];<br>p = 0.340 | Lesser benefit/added benefit not proven |
| Diarrhoea | Median: NA vs. NA<br>HR: 0.66 [0.40; 1.12];<br>p = 0.125 | Lesser benefit/added benefit not proven |

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| **Outcome category**<br>**Outcome** | **Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a]**<br>**Quantile of the time to event (months) or MD**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| Symptoms (EORTC QLQ-H&N35) | | |
| Pain<br>Disease status<br>Metastatic | Median: NA vs. NA<br>HR: 1.91 [1.18; 3.08];<br>HR[d]: 0.52 [0.32; 0.85];<br>p = 0.009<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>lesser benefit, extent: "minor" |
| Recurrent | Median: NA vs. NA<br>HR: 0.27 [0.08; 0.95];<br>p = 0.042 | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>lesser benefit/added benefit not proven[e] |
| Problems with swallowing | Median: NA vs. NA<br>HR: 0.94 [0.61; 1.45];<br>p = 0.791 | Lesser benefit/added benefit not proven |
| Problems with senses | Median: NA vs. NA<br>HR: 1.14 [0.81; 1.61];<br>p = 0.455 | Lesser benefit/added benefit not proven |
| Problems with speech | Median: NA vs. NA<br>HR: 0.92 [0.63; 1.34];<br>p = 0.663 | Lesser benefit/added benefit not proven |
| Problems with teeth | Median: NA vs. NA<br>HR: 0.83 [0.51; 1.34];<br>p = 0.444 | Lesser benefit/added benefit not proven |
| Problems with mouth opening | Median: NA vs. NA<br>HR: 0.80 [0.51; 1.26];<br>p = 0.337 | Lesser benefit/added benefit not proven |
| Dry mouth<br>Smoking status<br>Never or former | Median: ND vs. ND<br>HR: 0.56 [0.34; 0.93];<br>p = 0.024<br>probability: "hint" | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>lesser benefit/added benefit not proven[e] |
| Active | Median: NA vs. NA<br>HR: 1.84 [0.79; 4.31];<br>p = 0.159 | Lesser benefit/added benefit not proven |
| Sticky saliva | Median: NA vs. NA<br>HR: 1.10 [0.73; 1.65];<br>p = 0.659 | Lesser benefit/added benefit not proven |
| Cough | Median: NA vs. NA<br>HR: 0.91 [0.59; 1.42];<br>p = 0.685 | Lesser benefit/added benefit not proven |

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| **Outcome category**<br>**Outcome** | **Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a]**<br>**Quantile of the time to event (months) or MD**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| Feeling ill | | |
| Sex | | |
| Male | Median: NA vs. NA<br>HR: 0.91 [0.55; 1.50];<br>p = 0.717 | Lesser benefit/added benefit not proven |
| Female | Median: NA vs. NA<br>HR: 5.35 [1.52; 18.79];<br>HR[d]: 0.19 [0.05; 0.66];<br>p = 0.009<br>probability: "hint" | Outcome category "non-serious/non-severe symptoms/late complications" $CI_u < 0.80$<br>lesser benefit, extent: "considerable" |
| Health status (EQ-5D VAS) | Mean (week 9): 72.9 vs. 72.9<br>MD: 0.20 [−3.30; 3.70];<br>p = 0.910 | Lesser benefit/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 functional scales | | |
| Global health status | Median: NA vs. 13.4<br>HR: 1.31 [0.89; 1.93];<br>p = 0.168 | Lesser benefit/added benefit not proven |
| Physical functioning | | |
| Age | | |
| < 65 years | Median: NA vs. NA<br>HR: 1.75 [1.10; 2.77];<br>HR[d]: 0.57 [0.36; 0.91];<br>p = 0.018 | Outcome category: health-related quality of life<br>$0.90 \leq CI_u < 1.00$<br>lesser benefit, extent: "minor" |
| ≥ 65 years | Median: NA vs. 6.5<br>HR: 0.72 [0.42; 1.24];<br>p = 0.234 | Lesser benefit/added benefit not proven |
| Role functioning | Median: NA vs. NA<br>HR: 0.92 [0.66; 1.26];<br>p = 0.590 | Lesser benefit/added benefit not proven |
| Emotional functioning | Median: NA vs. NA<br>HR: 1.03 [0.63; 1.66];<br>p = 0.913 | Lesser benefit/added benefit not proven |

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| **Outcome category**<br>**Outcome** | **Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a]**<br>**Quantile of the time to event (months) or MD**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| Cognitive functioning | | |
| Sex | | |
| Male | Median: NA vs. NA<br>HR: 0.84 [0.55; 1.27];<br>p = 0.412 | Lesser benefit/added benefit not proven |
| Female | Median: 4.9 vs. NA<br>HR: 4.20 [1.39; 12.67];<br>HR[d]: 0.24 [0.08; 0.72];<br>p = 0.011<br>probability: "hint" | Outcome category: health-related quality of life<br>$CI_u < 0.75$, risk ≥ 5%<br>lesser benefit, extent: "major" |
| Social functioning | Median: NA vs. NA<br>HR: 0.77 [0.55; 1.09];<br>p = 0.141 | Lesser benefit/added benefit not proven |
| EORTC QLQ-H&N35 functional scales | | |
| Problems with social eating | | |
| Age | | |
| < 65 years | Median: NA vs. NA<br>HR: 1.78 [1.04; 3.05];<br>HR[d]: 0.56 [0.33; 0.96];<br>p = 0.036<br>probability: "hint" | Outcome category: health-related quality of life<br>$0.90 \leq CI_u < 1.00$<br>lesser benefit, extent: "minor" |
| ≥ 65 years | Median: NA vs. NA<br>HR: 0.54 [0.26; 1.12];<br>p = 0.099 | Lesser benefit/added benefit not proven |
| Problems with social contact | Median: NA vs. NA<br>HR: 0.82 [0.54; 1.23];<br>p = 0.334 | Lesser benefit/added benefit not proven |
| Reduced sexuality | Median: NA vs. NA<br>HR: 0.86 [0.61; 1.22];<br>p = 0.404 | Lesser benefit/added benefit not proven |
| **Side effects** | | |
| SAEs | Median: 3.1 vs. 10.6<br>HR: 1.39 [1.09; 1.77];<br>HR[d]: 0.72 [0.56; 0.92];<br>p = 0.007<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>greater harm, extent: "minor" |
| Severe AEs (CTCAE grade ≥ 3) | Median: 1.1 vs. 0.9<br>HR: 1.03 [0.85; 1.26];<br>p = 0.744 | Greater/lesser harm not proven |

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| **Outcome category**<br>**Outcome** | **Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a]**<br>**Quantile of the time to event (months) or MD**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| Discontinuation due to AEs | Median: NA vs. 39.3<br>HR: 1.24 [0.90; 1.71];<br>p = 0.196 | Greater/lesser harm not proven |
| Immune-related SAEs | Median: NA vs. NA<br>HR: 1.20 [0.52; 2.78];<br>p = 0.671 | Greater/lesser harm not proven |
| Immune-related severe AEs<br>(CTCAE grade ≥ 3) | Median: NA vs. NA<br>HR: 0.44 [0.23; 0.86];<br>p = 0.015<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>lesser harm, extent: "considerable" |
| Paronychia | Proportion of events: 0% vs. 12.2%<br>RR: 0.02 [0.00; 0.28];<br>p = 0.001<br>probability: "indication"[f] | Outcome category: non-serious/non-severe side effects<br>$CI_u < 0.80$<br>lesser harm, extent: "considerable" |
| Skin and subcutaneous tissue disorders<br>(CTCAE grade ≥ 3) | Median: NA vs. NA<br>HR: 0.26 [0.11; 0.61];<br>p = 0.002<br>probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u < 0.75$, risk ≥ 5%<br>lesser harm, extent: "major" |
| Anaemia (PT, AEs [CTCAE grade ≥ 3]) | Proportion of events: 24.1% vs. 14.7%<br>RR: 1.64 [1.12; 2.39]<br>RR[d]: 0.61 [0.42; 0.89];<br>p = 0.010<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>greater harm, extent: "considerable" |
| Stomatitis<br>(CTCAE grade ≥ 3) | Proportion of events: 8.4% vs. 3.7%<br>RR: 2.30 [1.07; 4.94]<br>RR[d]: 0.43 [0.20; 0.93];<br>p = 0.028<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>greater harm, extent: "minor" |
| Mucosal inflammation<br>(CTCAE grade ≥ 3) | Proportion of events: 10.5% vs. 5.3%<br>RR: 1.99 [1.04; 3.79];<br>RR[d]: 0.50 [0.26; 0.96];<br>p = 0.034<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>greater harm, extent: "minor" |
| Respiratory, thoracic and mediastinal disorders<br>(CTCAE grade ≥ 3) | Median: NA vs. NA<br>HR: 1.91 [1.08; 3.38];<br>HR[d]: 0.52 [0.30; 0.93];<br>p = 0.027<br>probability: "hint" | Outcome category: serious/severe side effects<br>$0.90 \leq CI_u < 1.00$<br>greater harm, extent: "minor" |

Table 18: Extent of added benefit at outcome level: pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a] (multipage table)

| **Outcome category**<br>**Outcome** | **Pembrolizumab + chemotherapy[a] vs. cetuximab + chemotherapy[a]**<br>**Quantile of the time to event (months) or MD**<br>**Effect estimation [95% CI]; p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| a. Carboplatin or cisplatin + 5-FU.<br>b. Probability provided if a statistically significant and relevant effect is present.<br>c. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval ($CI_u$).<br>d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.<br>e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.<br>f. The certainty of results is considered high, as the observation of such a large effect is not explicable alone by different observation periods and potentially informative reasons.<br>5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; $CI_u$: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: mean difference; NA: not achieved; ND: no data; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus | | |

### 2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 19: Positive and negative effects from the assessment of pembrolizumab + chemotherapy[a] in comparison with cetuximab + chemotherapy[a]

| **Positive effects** | **Negative effects** |
|---|---|
| Mortality<br>▪ Overall survival:<br>hint of added benefit – extent "major" | |
| | Morbidity<br>Non-serious/non-severe symptoms/late complications<br>▪ Symptoms (EORTC QLQ-C30) – fatigue:<br>▫ For female patients:<br>hint of lesser benefit – extent: "minor"<br>▪ Symptoms (EORTC QLQ-H&N35) – pain:<br>▫ For patients with metastatic disease status:<br>hint of lesser benefit – extent: "minor"<br>▪ Symptoms (EORTC QLQ-H&N35) – feeling ill:<br>▫ For female patients:<br>hint of lesser benefit – extent: "considerable" |
| | Health-related quality of life<br>▪ EORTC QLQ-C30 (functional scale) – physical functioning and EORTC QLQ-H&N35 (functional scale) – problems with social eating<br>▫ In each case: for patients under the age of 65 years:<br>hint of lesser benefit – extent: "minor"<br>▪ EORTC QLQ C30 (functional scale) – cognitive functioning:<br>▫ For female patients:<br>hint of lesser benefit – extent: "major" |
| Serious/severe side effects<br>▪ Immune-related severe AEs (CTCAE grade ≥ 3):<br>hint of lesser harm – extent: "considerable"<br>▪ Skin and subcutaneous tissue disorders (CTCAE grade ≥ 3):<br>hint of lesser harm – extent "major"<br><br>Non-serious/non-severe side effects<br>▪ Paronychia:<br>indication of lesser harm – extent "considerable" | Serious/severe side effects<br>▪ SAEs:<br>hint of greater harm – extent: "minor"<br>▪ Anaemia (CTCAE grade ≥ 3):<br>hint of greater harm – extent: "considerable"<br>▪ Specific severe AEs (CTCAE grade ≥ 3), in each case hint of greater harm – extent: "minor":<br>▫ stomatitis (CTCAE grade ≥ 3)<br>▫ mucosal inflammation (CTCAE grade ≥ 3)<br>▫ respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3) |
| a. Carboplatin or cisplatin + 5-FU.<br>5-FU: 5-fluorouracil; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Cancer 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35, SAE: serious adverse event | |

Overall, partly only for subgroups, several positive and negative effects were shown, each with the probability “hint” or “indication” and with different extent.

A hint of an added benefit with the extent “major” was shown for overall survival.

In the outcome category of serious/severe side effects, a hint of lesser harm with the extent “considerable” or “major” was shown both for immune-related severe AEs (CTCAE grade ≥ 3) and for skin and subcutaneous tissue disorders. It should be noted that there was relevant overlap between both outcomes in terms of events included. A further positive effect with the extent “considerable” was shown in the outcome category of non-serious/non-severe side effects.

The positive effects were accompanied by hints of negative effects, each with the extent “minor” or “considerable”, in the overall rate of SAEs and in several specific severe AEs. It should also be noted that, for the outcome categories of morbidity and health-related quality of life, exclusively negative effects, each with the extent “minor” to “major”, were shown for different subgroups. In the overall consideration, this resulted in a downgrading of the extent of the added benefit.

In summary, there is a hint of considerable added benefit of pembrolizumab + chemotherapy versus the ACT for adults with metastatic or unresectable recurrent HNSCC whose tumours express PD-L1 with a CPS ≥ 1.

The result of the assessment of the added benefit of pembrolizumab + chemotherapy in comparison with the ACT is summarized in Table 20.

Table 20: Pembrolizumab + chemotherapy[a] – probability and extent of added benefit

| **Therapeutic indication** | **ACT[b]** | **Probability and extent of added benefit** |
|---|---|---|
| First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1[c] | **Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU**<br>*or*<br>radiochemotherapy with cisplatin ± 5-FU<br>(only for patients with locally advanced head and neck squamous cell carcinoma)<br>*or*<br>cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy<br>(only for patients with locally advanced head and neck squamous cell carcinoma) | Hint of considerable added benefit[d] |

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. For the present therapeutic indication, it is assumed that in this patient group an intervention with curative intent is an exception and therefore no longer indicated. The G-BA also assumes that only patients whose disease progression did not occur within 6 months of completion of prior therapy with curative intent are eligible for platinum-containing therapy [1].
d. The KEYNOTE-048 study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. Furthermore, only patients were included who had completed a prior systemic therapy with curative intent ≥ 6 months at the start of the study and in whom progression had not occurred within 6 months of completion of prior therapy with curative intent.

5-FU: 5-fluorouracil; 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 assessment described above deviates from that of the company, which claimed an indication of major added benefit.

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

## 2.6 List of included studies

Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, De Castro G Jr et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019; 394(10212): 1915-1928.

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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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