IQWiG Reports – Commission No. A19-100

Pembrolizumab (head and neck squamous cell carcinoma, monotherapy) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Pembrolizumab (Plattenepithelkarzinom der Kopf-Hals-Region, Monotherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[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
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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 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

Therapeutic indication	**ACT**[a]
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[b]	**Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU** *or* radiochemotherapy with cisplatin ± 5-FU (only for patients with locally advanced head and neck squamous cell carcinoma) *or* cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy (only for patients with locally advanced head and neck squamous cell carcinoma)
a. 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**. b. 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-fluorouracil (5-FU) or cetuximab + cisplatin + 5-FU as comparator therapy. Hereinafter, the comparator therapy is referred to as "cetuximab + 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.

301 (pembrolizumab) and 300 (cetuximab + chemotherapy) patients were randomly allocated to the study arms relevant for the present benefit assessment. Of these, the subpopulation of patients with PD-L1-expressing tumour with CPS ≥ 1 is relevant (257 in the pembrolizumab arm and 255 in the cetuximab + chemotherapy arm).

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 adverse events (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 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 and due to the large proportion of patients not included in the analysis. 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 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". When looking at the Kaplan-Meier curves for this outcome, it is noticeable that the Kaplan-Meier curves cross each other: The pembrolizumab arm shows a stronger decrease of the Kaplan-Meier curve in the first 7 months than the cetuximab + chemotherapy arm. The Kaplan-Meier curves cross at about 8 months after the start of the study; the advantage of pembrolizumab only becomes apparent afterwards. This suggests the possible presence of an effect modification.

The investigation of subgroups shows an effect modification by the characteristic "disease status". Kaplan-Meier curves for the corresponding subgroups were not available in the dossier.

The effect modification resulted in a hint of an added benefit of pembrolizumab versus the ACT for adults with metastatic disease. For adults with (unresectable) recurrent disease, in contrast, there was no hint of an added benefit of pembrolizumab versus the ACT; an added benefit is not proven for these patients.

Morbidity

Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35)

No usable analyses were available for symptoms recorded with the symptom scales of the cancer-specific instrument European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Cancer 30 (QLQ-C30) and of the instrument specific for head and neck tumours, the EORTC Quality of Life Questionnaire-Head and Neck Cancer 35 (QLQ-H&N35). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

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

No usable analyses were available for health-related quality of life recorded with the functional scales and the scale for recording global health status of the cancer-specific instrument EORTC QLQ-C30 and of the disease-specific instrument EORTC QLQ-H&N35 (functional scales). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

Side effects

Serious adverse events

No statistically significant difference between the treatment groups was shown for the outcome "serious adverse events (SAEs)". This resulted in no hint of greater or lesser harm of pembrolizumab versus the ACT; greater or lesser harm is therefore not proven.

Severe adverse events (CTCAE grade ≥ 3)

A statistically significant difference in favour of pembrolizumab versus the ACT was shown for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab in comparison with the ACT.

Discontinuation due to adverse events

A statistically significant difference in favour of pembrolizumab was shown for the outcome "discontinuation due to AEs". However, there was an effect modification by the characteristic "region". Only the subgroup of patients of the region of Europe was considered because this is the one decisive for the present benefit assessment. This resulted in a hint of lesser harm from pembrolizumab in comparison with the ACT.

Specific adverse events

Immune-related serious adverse events and immune-related severe adverse events (CTCAE grade ≥ 3)

No statistically significant difference between the treatment groups was shown for the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". In each case, this resulted in no hint of greater or lesser harm of pembrolizumab versus the ACT; greater or lesser harm is therefore not proven.

Paronychia and blood and lymphatic system disorders (CTCAE grade ≥ 3)

Statistically significant differences in favour of pembrolizumab were shown for the outcomes "paronychia" and "blood and lymphatic system disorders (CTCAE grade ≥ 3)". Despite the

high risk of bias, the certainty of results was not downgraded in these outcomes. In each case, this resulted in an indication of lesser harm from pembrolizumab in comparison with the ACT.

Skin and subcutaneous tissue disorders (CTCAE grade ≥ 3), ear and labyrinth disorders, asthenia, dizziness, anaemia (CTCAE grade ≥ 3), gastrointestinal disorders (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), investigations (CTCAE grade ≥ 3) and hypomagnesaemia (CTCAE grade ≥ 3)

Statistically significant differences in favour of pembrolizumab in comparison with cetuximab + chemotherapy were shown for the following outcomes: skin and subcutaneous tissue disorders (CTCAE grade ≥ 3), ear and labyrinth disorders, asthenia, dizziness, anaemia (CTCAE grade ≥ 3), gastrointestinal disorders (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), investigations (CTCAE grade ≥ 3) and hypomagnesaemia (CTCAE grade ≥ 3). In each case, this resulted in a hint of lesser harm from pembrolizumab in comparison with the ACT.

Respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab in comparison with cetuximab + chemotherapy was shown for the outcome "respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)". This resulted in a hint of greater harm from pembrolizumab 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, the extent and probability of the added benefit of the drug pembrolizumab compared with the ACT is assessed as follows:

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

The positive effects in overall survival were only shown in patients with metastatic disease. For this reason, the balancing of positive and negative effects below is conducted separately by disease status.

Patients with metastatic disease

Positive effects in overall survival were shown for patients with metastatic disease status. No Kaplan-Meier curves were available for the subgroups; these would be necessary for the

[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].

assessment of the extent of added benefit. This is due to the intersecting course of the Kaplan-Meier curves for overall survival of the total population. Based on the data presented, it remains unclear to what extent the characteristic “disease status” is an explanatory factor for this course of the curves and thus also whether the hazard ratio (HR) presented is an adequate representation of the effect over the total observation period. For this reason, the extent of the added benefit for patients with metastatic disease is non-quantifiable.

In addition, further positive effects in the outcome categories of serious/severe side effects and non-serious/non-severe side effects, partly with the extent “major”, were shown for patients with metastatic disease. These positive effects were accompanied by greater harm with the extent “minor” in the specific AE “severe respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)”. No usable results were available for the outcome category “health-related quality of life” and for symptoms.

Overall, the positive effects predominate, which are not called into question by the negative effect. In summary, there is a hint of a non-quantifiable, but (due to the advantages in the outcome category of side effects) at least considerable added benefit of pembrolizumab versus the ACT for adults with metastatic HNSCC whose tumours express PD-L1 with a CPS ≥ 1.

Patients with recurrent disease

Positive effects were shown for patients with (unresectable) recurrent disease status, but only in the outcome categories of serious/severe side effects and non-serious/non-severe side effects. As was the case for patients with metastatic disease, these positive effects were accompanied by greater harm with the extent “minor” in the specific AE “severe respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)”. It should also be noted that no usable results were available for the outcome category “health-related quality of life” and for symptoms.

Overall, there was a hint of considerable added benefit of pembrolizumab in comparison with the ACT for patients with recurrent disease status.

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

Table 3: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**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[b]	**Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU** *or* radiochemotherapy with cisplatin ± 5-FU (only for patients with locally advanced head and neck squamous cell carcinoma) *or* cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy (only for patients with locally advanced head and neck squamous cell carcinoma)	
With metastatic disease status		Hint of non-quantifiable, but at least considerable added benefit[c]
With recurrent disease status		Hint of considerable added benefit[c]

a. 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**.
b. 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].
c. 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; 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 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

Therapeutic indication	**ACT**[a]
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[b]	**Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU** *or* radiochemotherapy with cisplatin ± 5-FU (only for patients with locally advanced head and neck squamous cell carcinoma) *or* cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy (only for patients with locally advanced head and neck squamous cell carcinoma)
a. 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**. b. 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".

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 (status: 7 October 2019)
- bibliographical literature search on pembrolizumab (last search on 7 October 2019)

- search in trial registries for studies on pembrolizumab (last search on 14 October 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (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 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 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) pembrolizumab + chemotherapy[a] (N = 281)[d] cetuximab + chemotherapy[a] (N = 300) Relevant subpopulation thereof/subpopulation thereof analysed by the company[e]: pembrolizumab (n = 257) cetuximab + chemotherapy[a] (n = 255)	Screening: up to 28 days Treatment: until radiological disease progression, unacceptable side effect, investigator's/patient's decision at most 24 months[f, g] Observation[h]: outcome-specific, at most until death, withdrawal of consent or end of the study	228 study centres in: 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 4/2015–ongoing Data cut-offs: Interim analysis I: 17 Oct 2017 Interim analysis II: 13 Jun 2018 Final data cut-off: 25 Feb 2019	Primary: overall survival, PFS Secondary: symptoms, health status, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab 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).
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.
c. Systemic 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.
d. The arm is not relevant for the assessment and is not shown in the next tables.
e. Adult patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS ≥ 1.
f. Patients in the pembrolizumab 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.
g. 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.
h. Outcome-specific information is provided in Table 8.

5-FU: 5-fluorouracil; AE: adverse event; CPS: combined positive score; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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 vs. cetuximab + chemotherapy[a] (multipage table)

Study	Intervention	Comparison
KEYNOTE-048	Pembrolizumab 200 mg IV every 3 weeks, for a maximum of 24 months	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 + ▪ cisplatin[b] 100 mg/m² BSA IV every 3 weeks, for a maximum of 6 cycles *or* ▪ carboplatin[b] AUC 5 IV, every 3 weeks, for a maximum of 6 cycles + 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 adjustment not allowed ▪ Interruption or treatment discontinuation in case of AEs in compliance with the SPC	▪ Dose adjustment, interruption or treatment discontinuation for cetuximab, carboplatin, cisplatin and 5-FU without relevant deviations from the SPC
	Pretreatment not allowed: ▪ systemic therapy in the metastatic or recurrent setting ▪ radiotherapy or other non-systemic therapy within 2 weeks prior to randomization ▪ investigational preparations within 4 weeks before first dose of study medication ▪ 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) ▪ prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent ▪ live vaccines within 30 days prior to the first dose of study medication allowed: ▪ systemic therapy as part of combination therapy for locally advanced cancer which was completed ≥ 6 months before start of the study **Concomitant treatment** not allowed: ▪ antineoplastic systemic chemotherapy or biologic therapy ▪ other immunotherapy or chemotherapy not conforming to the protocol ▪ other investigational preparations ▪ radiotherapy (exception: individual symptomatic lesions or brain radiation); palliative radiotherapy was analysed as clinical progression ▪ live vaccines (allowed in the comparator arm) ▪ systemic corticosteroids, see allowed concomitant treatment for exceptions allowed: ▪ premedication for the platinum-based combination chemotherapy used in the study: dexamethasone ≤ 8 mg on day 1 of a cycle before study medication ▪ premedication for cetuximab: H1 antagonist before the first dose ▪ 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	

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

Study	Intervention	Comparison
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.

301 patients were randomly allocated to treatment with pembrolizumab, 281 to treatment with pembrolizumab + chemotherapy, 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 using the CINtec p16 histology assay and a 70% cut-off); HPV status was assumed negative for all other locations.

The study arms with pembrolizumab and with cetuximab + chemotherapy were relevant for the research question of the present benefit assessment; the study arm with pembrolizumab + chemotherapy 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 ≥ 1 is relevant for the present benefit assessment [4,5].

The company presented analyses for this subpopulation (257 patients in the pembrolizumab arm versus 255 in the cetuximab + chemotherapy arm). In the following, only the relevant subpopulation will be discussed, unless otherwise stated.

Treatment of the patients with pembrolizumab was in compliance with the SPC [4,5]. 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, which is also cited by the SPC on cetuximab for the combination of cetuximab + chemotherapy [6,7]. Treatment with cetuximab + chemotherapy was therefore largely in compliance with the SPCs [7-10].

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 could additionally receive a second treatment with pembrolizumab 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 for at least 24 weeks and that (during the course of the study) there was a complete response to pembrolizumab, 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 3 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 a maximum of 24 months, whereas treatment with carboplatin or cisplatin and 5-FU was ended after 6 cycles of 3 weeks at the latest.

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 vs. cetuximab + chemotherapy[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE-048	
Mortality	
Overall survival	Up to death, withdrawal of consent or end of study, whichever is first
Morbidity	
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 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. 3 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 vs. cetuximab + chemotherapy[a] (multipage table)

Study Characteristics Category	Pembrolizumab N = 257	Cetuximab + chemotherapy[a] N = 255
KEYNOTE-048		
Age [years], mean (SD)	61 (10)	61 (10)
Sex [F/M], %	19/81	14/86
Family origin, n (%)		
White	188 (73.2)	189 (74.1)
Non-white	67 (26.1)	65 (25.5)
Missing	2 (0.8)	1 (0.4)
Region, n (%)		
North America	68 (26.5)	54 (21.2)
Europe	74 (28.8)	92 (36.1)
Rest of the world	115 (44.7)	109 (42.7)
Smoking status, n (%)		
Never	59 (23.0)	61 (23.9)
Former	154 (59.9)	156 (61.2)
Active	44 (17.1)	36 (14.1)
Missing	0 (0.0)	2 (0.8)
ECOG PS, n (%)		
0	104 (40.5)	101 (39.6)
1	153 (59.5)	154 (60.4)
HPV status, n (%)		
Positive	54 (21.0)	55 (21.6)
Negative	203 (79.0)	200 (78.4)
PD-L1 TPS status, n (%)		
TPS < 50%	190 (73.9)	189 (74.1)
TPS ≥ 50%	67 (26.1)	66 (25.9)
PD-L1 CPS status, n (%)		
CPS < 20	123 (47.9)	131 (51.4)
CPS ≥ 20	133 (51.8)	122 (47.8)
Missing	1 (0.4)	2 (0.8)
Disease status, n (%)		
Metastatic	179 (69.6)	168 (65.9)
Recurrent	75 (29.2)	84 (32.9)
Other	3 (1.2)	3 (1.2)
Presence of brain metastases, n (%)	1 (0.4)	1 (0.4)
Disease stage, n (%)		
II	1 (0.4)	1 (0.4)
III	10 (3.9)	11 (4.3)
IVA	56 (21.8)	57 (22.4)

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

Study Characteristics Category	Pembrolizumab N = 257	Cetuximab + chemotherapy[a] N = 255
IVB	11 (4.3)	18 (7.1)
IVC	179 (69.6)	168 (65.9)
Location of primary tumour[b], n (%)		
Oral cavity	75 (29.2)	80 (31.4)
Larynx	57 (22.2)	53 (20.8)
Hypopharynx	34 (13.2)	32 (12.5)
Oropharynx	97 (37.7)	94 (36.9)
Time from prior systemic therapy [months][c]		
Mean (SD)	26.6 (33.8)[d]	27.8 (27.8)[d]
Median [Q1; Q3]	16.7 [11.2; 26.8][d]	20.6 [11.5; 33.2][d]
Time from prior platinum-containing therapy [months][e]		
Mean (SD)	24.8 (22.2)[d]	28.3 (28.4)[d]
Median [Q1; Q3]	16.8 [11.6; 27.5][d]	19.2 [11.5; 34.9][d]
Time from initial diagnosis of the disease [months]		
Mean (SD)	37.7 (56.5)	31.0 (36.4)
Median [Q1; Q3]	19.4 [11.5; 39.7]	20.1 [11.7; 38.5]
Treatment discontinuation[f, g], n (%)	225 (87.9)	238 (97.1)
Study discontinuation[g, h], n (%)	12 (4.7)	16 (6.3)

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. For one patient, several locations were possible.
c. The information is based on 130 (50.6%) patients in the pembrolizumab arm and 125 (49.0%) patients in the cetuximab + chemotherapy arm.
d. Institute's calculation from days into months.
e. The information is based on 112 (43.6%) patients in the pembrolizumab arm and 120 (47.1%) patients in the cetuximab + chemotherapy arm.
f. At the data cut-off from 25 February 2019, a total of 31 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 7 patients in the comparator arm were receiving ongoing treatment.
b. Data cut-off: 25 February 2019.
h. Without deaths; reason for discontinuation in each case: "withdrawal of consent".

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 16% were still active smokers. In each case, just over 2 thirds of the relevant subpopulation had a metastatic and almost 1 third

a recurrent disease status. Both study arms included 3 patients each 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 vs. cetuximab + chemotherapy[a]

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab** **N = 257**	**Cetuximab + chemotherapy[a]** **N = 255**
KEYNOTE-048 (data cut-off 25 February 2019)		
Treatment duration [months][b]		
Median [Q1; Q3]	3.70 [1.45; 8.54]	4.86 [2.33; 7.39]
Mean (SD)	6.82 (7.48)	6.14 (6.66)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	12.2 [ND]	10.3 [ND]
Mean (SD)	ND	ND
Morbidity	ND	ND
Health-related quality of life	ND	ND
AEs[b, c]		
Median [Q1; Q3]	4.68 [2.43; 9.45]	5.85 [3.32; 8.38]
Mean (SD)	7.74 (7.53)	7.03 (6.60)
SAEs[b, c]		
Median [Q1; Q3]	6.44 [4.34; 11.27]	7.52 [4.86; 9.99]
Mean (SD)	9.25 (7.84)	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 N = 256, 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, 119 (46.3%) patients in the intervention arm received systemic follow-up therapy as their first subsequent treatment and 20 (7.8%) patients received radiotherapy as their first subsequent treatment. The respective numbers in the comparator arm were 128 (50.2%) and 19 (7.5%) patients. One patient per study arm 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 vs. cetuximab + chemotherapy[a] (multipage table)

Study **Drug class** **Drug**	**Patients with subsequent therapy n (%)**	
	Pembrolizumab **N = 257**	**Cetuximab + chemotherapy[b]** **N = 255**
KEYNOTE-048 (data cut-off 25 February 2019)		
Patients with ≥ 1 subsequent systemic therapy	119 (46.3)	128 (50.2)
Chemotherapy	110 (92.4[c])	93 (72.7[c])
Paclitaxel	51 (42.9[c])	44 (34.4[c])
Carboplatin	53 (44.5[c])	25 (19.5[c])
Fluorouracil	53 (44.5[c])	13 (10.2[c])
Cisplatin	48 (40.3[c])	12 (9.4[c])
Docetaxel	17 (14.3[c])	29 (22.7[c])
Methotrexate	15 (12.6[c])	11 (8.6[c])
Capecitabine	10 (8.4[c])	3 (2.3[c])
Gemcitabine	10 (8.4[c])	2 (1.6[c])
Gimeracil (+) oteracil (+) tegafur	7 (5.9[c])	0 (0)
Vinorelbine	2 (1.7[c])	2 (1.6[c])
Bleomycin	1 (0.8[c])	2 (1.6[c])
Cyclophosphamide	0 (0)	1 (0.8[c])
Epirubicin	1 (0.8[c])	0 (0)
Gimeracil	1 (0.8[c])	1 (0.8[c])
Hydroxyurea	1 (0.8[c])	0 (0)
Mitomycin	1 (0.8[c])	0 (0)
Nedaplatin	1 (0.8[c])	0 (0)
Tegafur	1 (0.8[c])	1 (0.8[c])
Vincristine	1 (0.8[c])	0 (0)
EGFR inhibitor	59 (49.6[c])	18 (14.1[c])
Cetuximab	57 (47.9[c])	18 (14.1[c])
Afatinib	2 (1.7[c])	0 (0)
Tarloxotinib bromide	1 (0.8)	0 (0)
Immune checkpoint inhibitors	16 (13.4[c])	62 (48.4[c])
Nivolumab	8 (6.7[c])	35 (27.3[c])
Pembrolizumab	9 (7.6[c])	16 (12.5[c])
Durvalumab	1 (0.8[c])	7 (5.5[c])
Tremelimumab	0 (0)	3 (2.3[c])
Atezolizumab	1 (0.8[c])	1 (0.8[c])
Avelumab	0 (0)	1 (0.8[c])
Cemiplimab	0 (0)	1 (0.8[c])
Enoblituzumab	1 (0.8[c])	0 (0)
Ipilimumab	1 (0.8[c])	1 (0.8[c])

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

Study	**Patients with subsequent therapy n (%)**	
Drug class **Drug**	**Pembrolizumab** **N = 257**	**Cetuximab + chemotherapy[b]** **N = 255**
Kinase inhibitor	5 (4.2[c])	1 (0.8[c])
Palbociclib	3 (2.5[c])	0 (0)
ATR serine/threonine kinase inhibitor (unspecified)	1 (0.8[c])	1 (0.8[c])
Amcasertib	1 (0.8[c])	0 (0)
Other	2 (1.7[c])	4 (1.6[c])
CXCR2 inhibitor (unspecified)	0 (0)	1 (0.8[c])
L-006097405	0 (0)	1 (0.8[c])
Antineoplastic (unspecified)	1 (0.8[c])	0 (0)
Bevacizumab	1 (0.8[c])	1 (0.8[c])
Investigational preparation (unspecified)	0 (0)	1 (0.8[c])
Other immunotherapies	2 (1.7[c])	3 (2.3[c])
Anti-ICOS monoclonal antibody (unspecified)	1 (0.8[c])	0 (0)
Axalimogene filolisbac	1 (0.8[c])	0 (0)
Epacadostat	0 (0)	1 (0.8[c])
mRNA vaccine	1 (0.8[c])	0 (0)
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 A, 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; EGFR: epidermal growth factor receptor; ICOS: inducible costimulator molecule; mRNA: messenger RNA; n: number of patients with subsequent therapy; N: number of analysed patients in the relevant subpopulation with CPS ≥ 1; RCT: randomized controlled trial; RNA: ribonucleic acid; vs.: versus

In the KEYNOTE-048 study, almost 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 mainly recommend programmed cell death 1 (PD-1) inhibitors such as nivolumab or pembrolizumab as subsequent therapies (second line), 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 (second line and above) 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 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 A) (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 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	No[c]	Yes	No[c]	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]), ear and labyrinth disorders (SOC, AEs), asthenia (PT, AEs), dizziness (PT, AEs), blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3]), anaemia (PT, AEs [CTCAE grade ≥ 3]), gastrointestinal disorders (SOC, AEs [CTCAE grade ≥ 3]), mucosal inflammation (PT, AEs [CTCAE grade ≥ 3]), investigations [SOC, AEs [CTCAE grade ≥ 3]), hypomagnesaemia (PT, AEs [CTCAE grade ≥ 3]), respiratory, thoracic and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3]).
c. No usable data available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.

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 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]	-[d]	H[e, f]	-[d]	H[g]	H[e]	H[g]	H[g]	H[e, g, h]

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]), ear and labyrinth disorders (SOC, AEs), asthenia (PT, AEs), dizziness (PT, AEs), blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3]), anaemia (PT, AEs [CTCAE grade ≥ 3]), gastrointestinal disorders (SOC, AEs [CTCAE grade ≥ 3]), mucosal inflammation (PT, AEs [CTCAE grade ≥ 3]), investigations [SOC, AEs [CTCAE grade ≥ 3]), hypomagnesaemia (PT, AEs [CTCAE grade ≥ 3]), 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. No usable data available (see Section 2.7.4.3.2 of the full dossier assessment).
e. Lack of blinding in subjective recording of outcomes (in the case of AEs, this aspect only concerns non-serious/non-severe AEs).
f. Large proportion of patients not included in the analysis.
g. Incomplete observations for potentially informative reasons.
h. Important difference in the median observation period between the intervention arm (4.68 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.

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 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), ear and labyrinth disorders, asthenia, dizziness, blood and lymphatic system disorders (CTCAE grade ≥ 3), anaemia (CTCAE grade ≥ 3), gastrointestinal disorders (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), investigations (CTCAE grade ≥ 3), hypomagnesaemia (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 between control and intervention arm 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 "ear and labyrinth disorders", "asthenia" and "dizziness", the lack of blinding in subjective recording of outcomes was an additional factor for the high risk of bias.

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 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.

Kaplan-Meier curves on 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 vs. cetuximab + chemotherapy[a] (multipage table)

Study Outcome category Outcome	Pembrolizumab		Cetuximab + chemotherapy[a]		Pembrolizumab vs. cetuximab + chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p-value[c]
KEYNOTE-048 (data cut-off 25 February 2019)					
Mortality					
Overall survival	257	12.3 [10.8; 14.3] 197 (76.7)	255	10.3 [9.0; 11.5] 229 (89.8)	0.74 [0.61; 0.90]; 0.003
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales)				No usable data	
Symptoms (EORTC QLQ-H&N35 symptom scales)				No usable data	
Health-related quality of life					
EORTC QLQ-C30 (functional scales and global health status scale)				No usable data	
EORTC QLQ-H&N35 (functional scales)				No usable data	
Side effects					
AEs (supplementary information)	*256*	*0.5 [0.3; 0.6]*[d] *248 (96.9)*	*245*	*0.4 [0.1; 0.1]*[d] *244 (99.6)*	–
SAEs	256	21.4 [9.7; NC][d] 106 (41.4)	245	10.6 [5.2; NC][d] 121 (49.4)	0.78 [0.60; 1.02][e]; 0.067
Severe AEs (CTCAE grade ≥ 3)	256	5.5 [3.2; 9.0][d] 140 (54.7)	245	0.9 [0.7; 1.2][d] 203 (82.9)	0.41 [0.33; 0.51][e]; < 0.001
Discontinuation due to AEs	256	NA 30 (11.7)	245	39.3 [39.3; NC][d] 67 (27.3)	0.39 [0.25; 0.60][e]; < 0.001
Immune-related AEs (supplementary information)[f]	*256*	*10.4 [9.0; 21.4]*[d] *81 (31.6)*	*245*	*NA* *59 (24.1)*	–
Immune-related SAEs	256	NA 18 (7.0)	245	NA 10 (4.1)	1.66 [0.76; 3.61][e]; 0.204
Immune-related severe AEs (CTCAE grade ≥ 3)	256	NA 21 (8.2)	245	NA 27 (11.0)	0.65 [0.36; 1.16][e]; 0.142
Paronychia (PT, AEs)	256	ND 1 (0.4)	245	ND 30 (12.2)	RR: 0.03 [0.0; 0.23][g]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs [CTCAE grade ≥ 3])	256	NA 10 (3.9)	245	NA 24 (9.8)	0.37 [0.17; 0.77][e]; 0.008

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

Study Outcome category Outcome	Pembrolizumab		Cetuximab + chemotherapy[a]		Pembrolizumab vs. cetuximab + chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p-value[c]
Ear and labyrinth disorders (SOC, AEs)	256	NA 21 (8.2)	245	NA [33.3; NC][d] 44 (18.0)	0.44 [0.26; 0.75][e]; 0.002
Asthenia (PT, AEs)	256	ND 13 (5.1)	245	ND 32 (13.1)	RR: 0.39 [0.21; 0.72][g]; 0.002
Dizziness (PT, AEs)	256	ND 12 (4.7)	245	ND 29 (11.8)	RR: 0.40 [0.21; 0.76][g]; 0.004
Blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3])	256	NA 15 (5.9)	245	NA 90 (36.7)	0.13 [0.08; 0.23][e]; < 0.001
Anaemia (PT, AEs [CTCAE grade ≥ 3])	256	ND 12 (4.7)	245	ND 36 (14.7)	RR: 0.32 [0.17; 0.60][g]; < 0.001
Gastrointestinal disorders (SOC, AEs [CTCAE grade ≥ 3])	256	NA 18 (7.0)	245	NA 42 (17.1)	0.38 [0.22; 0.67][e]; < 0.001
Mucosal inflammation (PT, AEs [CTCAE grade ≥ 3])	256	ND 4 (1.6)	245	ND 13 (5.3)	RR: 0.29 [0.10; 0.89][g]; 0.022
Investigations (SOC, AEs [CTCAE grade ≥ 3])[h]	256	NA 26 (10.2)	245	NA 55 (22.4)	0.42 [0.26; 0.67][e]; < 0.001
Hypomagnesaemia (PT, AEs [CTCAE grade ≥ 3])	256	ND 0 (0)	245	ND 10 (4.1)	RR: 0.05 [0.00; 0.77][g]; 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3])	256	NA 33 (12.9)	245	NA 18 (7.3)	1.82 [1.02; 3.24][e]; 0.042

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Unless stated otherwise: HR and 95% CI: Cox proportional hazards model stratified by ECOG PS, HPV status and PD-L1 status. If the number of events in a stratum was < 5, the stratification factors were cancelled successively (ECOG PS → HPV status → PD-L1 status) until the number of events in each stratum was ≥ 5.
c. p-value: Wald test.
d. Institute's calculation from weeks into months.
e. HR and 95% CI: Cox proportional hazards model.
f. See Section 2.7.4.3.2 of the full dossier assessment for reasons.
g. Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [14]).
h. Containing the following PTs with statistically significant difference between the treatment groups: "neutrophil count decreased" and "white blood cell count decreased".

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

Study Outcome category Outcome	Pembrolizumab		Cetuximab + chemotherapy[a]		Pembrolizumab vs. cetuximab + chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]; p-value[c]
5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; 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; SAE: serious adverse event; SOC: System Organ Class; vs.: versus					

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

Study Outcome category Outcome	Pembrolizumab			Cetuximab + chemotherapy[a]			Pembrolizumab 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]; p-value[c]
KEYNOTE-048							
Morbidity							
Health status (EQ-5D VAS)[d]	192	68 (18.5)	72.5 (18.4)	185	66.5 (19.9)	72 (16.8)	0.50 [−3.07; 4.07]; 0.783
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". When looking at the Kaplan-Meier curves for this outcome, it is noticeable that the Kaplan-Meier curves cross each other (see Section A.1, Figure 1, of the full dossier assessment): The pembrolizumab arm shows a stronger decrease of the Kaplan-Meier curve in the first 7 months than the cetuximab + chemotherapy arm. The Kaplan-Meier curves cross at about 8 months after the start of the study; the advantage of pembrolizumab only becomes apparent afterwards. This suggests the possible presence of an effect modification.

The investigation of subgroups shows an effect modification by the characteristic "disease status" (see Section 2.4.4). Kaplan-Meier curves for the corresponding subgroups were not available in the dossier.

The effect modification resulted in a hint of an added benefit of pembrolizumab versus the ACT for adults with metastatic disease. For adults with recurrent disease, in contrast, there was no hint of an added benefit of pembrolizumab versus the ACT; an added benefit is not proven for these patients.

This deviates from the assessment of the company, which saw an indication of an added benefit of pembrolizumab in comparison with the ACT for the outcome "overall survival" in the total relevant subpopulation.

Morbidity

Symptoms (EORTC QLQ-C30)

There were no usable analyses for symptoms recorded with the symptom scales of the cancer-specific instrument EORTC QLQ-C30 (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the results on the analyses of the time to first confirmed deterioration for the EORTC QLQ-C30 symptom scales. On the basis of these results and the other outcomes on morbidity, the company derived an overall hint of an added benefit for morbidity.

Symptoms (EORTC QLQ-H&N35)

There were no usable analyses for symptoms recorded with the symptom scales of the instrument EORTC QLQ-H&N35 specific for head and neck tumours (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

This deviates from the assessment of the company, which used the results on the analyses of the time to first confirmed deterioration for the EORTC QLQ-H&N35 symptom scales. On the

basis of these results and the other outcomes on morbidity, the company derived an overall hint of an added benefit for morbidity.

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 in comparison with the ACT; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as it also derived no advantage or disadvantage for this outcome; however, it used the analyses on the time to first confirmed deterioration by ≥ 7 or ≥ 10 points for this purpose. On the basis of these results and the other outcomes on morbidity, the company derived an overall hint of an added benefit for morbidity.

Health-related quality of life

EORTC QLQ-C30 (functional scales and global health status scale) and EORTC QLQ-H&N35 (functional scales)

No usable analyses were available for health-related quality of life recorded with the functional scales and the scale for recording global health status of the cancer-specific instrument EORTC QLQ-C30 and of the disease-specific instrument EORTC QLQ-H&N35 (functional scales) (see Section 2.7.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab 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 as not proven for these outcomes; but it used the analyses of the time to first confirmed deterioration for this purpose and allocated the total 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 saw an indication of considerable added benefit for the total outcome category of side effects. It based this conclusion on the results on severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. Furthermore, it pointed out that 20 SOCs showed significant results in favour of pembrolizumab, whereas only 2 SOCs showed results to the disadvantage of pembrolizumab. At the level of individual outcomes, the company drew no conclusion on probability and extent of any greater or lesser harm.

Serious adverse events

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

Severe adverse events (CTCAE grade ≥ 3)

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

Discontinuation due to adverse events

A statistically significant difference in favour of pembrolizumab was shown for the outcome "discontinuation due to AEs". However, there was an effect modification by the characteristic "region" (see Section 2.4.4). Only the subgroup of patients of the region of Europe was considered because this is the one decisive for the present benefit assessment. This resulted in a hint of lesser harm from pembrolizumab in comparison with the ACT.

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 versus the ACT; greater or lesser harm is therefore not proven.

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

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

Paronychia and blood and lymphatic system disorders (CTCAE grade ≥ 3)

Statistically significant differences in favour of pembrolizumab were shown for the outcomes "paronychia" and "blood and lymphatic system disorders (CTCAE grade ≥ 3)". Despite the high risk of bias, the certainty of results was not downgraded in these outcomes (see Section 2.7.4.2 of the full dossier assessment). In each case, this resulted in an indication of lesser harm from pembrolizumab in comparison with the ACT.

Skin and subcutaneous tissue disorders (CTCAE grade ≥ 3), ear and labyrinth disorders, asthenia, dizziness, anaemia (CTCAE grade ≥ 3), gastrointestinal disorders (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), investigations (CTCAE grade ≥ 3) and hypomagnesaemia (CTCAE grade ≥ 3)

Statistically significant differences in favour of pembrolizumab in comparison with cetuximab + chemotherapy were shown for the following outcomes: skin and subcutaneous tissue disorders (CTCAE grade ≥ 3), ear and labyrinth disorders, asthenia, dizziness, anaemia

(CTCAE grade ≥ 3), gastrointestinal disorders (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), investigations (CTCAE grade ≥ 3) and hypomagnesaemia (CTCAE grade ≥ 3). In each case, this resulted in a hint of lesser harm from pembrolizumab in comparison with the ACT.

Respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab in comparison with cetuximab + chemotherapy was shown for the outcome "respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)". This resulted in a hint of greater harm from pembrolizumab 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, there had to be 10 events in at least one 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 (mortality, side effects) – RCT, direct comparison: pembrolizumab vs. cetuximab + chemotherapy[a](multipage table)

Study Outcome	Pembrolizumab		Cetuximab + chemotherapy[a]		Pembrolizumab vs. cetuximab + chemotherapy[a]	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]	p-value[c]
KEYNOTE-048 (data cut-off 25 February 2019)						
Mortality						
Overall survival						
Disease status						
Metastatic	179	13.1 [10.8; 16.8] 132 (73.7)	168	9.7 [8.5; 11.2] 153 (91.1)	0.62 [0.49; 0.79]	< 0.001
Recurrent	75	11.5 [7.8; 13.0] 64 (85.3)	84	12.1 [9.2; 13.9] 74 (88.1)	1.04 [0.74; 1.45]	0.835
Total					Interaction:	0.016[d]
Side effects						
Severe AEs (CTCAE grade ≥ 3)						
Sex						
Male	208	25.3 [14.1; 42.0] 113 (54.3)	211	5.1 [4.1; 6.0] 170 (80.6)	0.44 [0.35; 0.56][e]	< 0.001
Female	48	18.3 [8.4; 93.1] 27 (56.3)	34	2.0 [1.1; 2.4] 33 (97.1)	0.22 [0.13; 0.39][e]	< 0.001
Total					Interaction:	0.028[d]
Discontinuation due to AEs						
Region						
North America	68	NA 3 (4.4)	49	NA [50.6; NC] 16 (32.7)	0.12 [0.04; 0.42][e]	< 0.001
Europe	73	NA 6 (8.2)	90	NA [37.3; NC] 30 (33.3)	0.20 [0.08; 0.48][e]	< 0.001
Rest of the world	115	NA [93.1; NC] 21 (18.3)	106	NA [171.0; NC] 21 (19.8)	0.94 [0.51; 1.74][e]	0.841
Total					Interaction:	0.001[d]

a. Carboplatin + 5-FU or cisplatin + 5-FU.
b. Unless stated otherwise: HR and 95% CI: Cox proportional hazards model stratified by ECOG PS, HPV status and PD-L1 status. If the number of events in a stratum was < 5, the stratification factors were cancelled successively (ECOG PS → HPV status → PD-L1 status) until the number of events in each stratum was ≥ 5.
c. p-value: Wald test.
d. Q test.
e. HR and 95% CI: Cox proportional hazards model.

Table 17: Subgroups (mortality, side effects) – RCT, direct comparison: pembrolizumab vs. cetuximab + chemotherapy[a](multipage table)

Study Outcome	Pembrolizumab		Cetuximab + chemotherapy[a]		Pembrolizumab vs. cetuximab + chemotherapy[a]	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]	p-value[c]
5-FU: 5-fluorouracil; AE: adverse event; CI: confidence interval; CPS: combined positive score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus						

Mortality

Overall survival

For the outcome "overall survival", there were effect modifications by the characteristics of PD-L1 status (CPS < 20 vs. CPS ≥ 20) and disease status (metastatic vs. recurrent), which are described below.

PD-L1 status

No statistically significant difference for the outcome "overall survival" was shown for patients with CPS < 20 (see Appendix D, Table 29, of the full dossier assessment). For patients with CPS ≥ 20, a statistically significant difference in favour of the intervention was shown for overall survival. This is not reflected in the results on the second investigated characteristic on PD-L1 status (TPS < 50% versus TPS ≥ 50%), for which no effect modification was shown.

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

Disease status

For adults with metastatic disease status, a statistically significant difference in favour of pembrolizumab was shown for overall survival. For patients with (unresectable) recurrent disease status, in contrast, no statistically significant difference was shown. The Kaplan-Meier curves on overall survival of all included patients cross each other (see Section 2.4.3, and Section A.1, Figure 1, of the full dossier assessment). There are no Kaplan-Meier curves for the results on the subgroup characteristic "disease status". It therefore remains unclear to what

extent the characteristic of disease status is an explanatory factor for the course of overall survival in the total population or whether comparable courses are also found in the subgroups. Hence, it also remains unclear whether the HR presented adequately reflects the effect in the total observation period. The extent of the added benefit for patients with metastatic disease is therefore non-quantifiable. This resulted in a hint of an added benefit of pembrolizumab in comparison with the ACT for adults with metastatic disease status. For patients with (unresectable) recurrent disease status, there was no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven for this patient group.

Side effects

Severe adverse events (CTCAE grade ≥ 3)

There was an effect modification by the characteristic "sex" for the outcome "severe AEs (CTCAE grade ≥ 3)". A statistically significant difference in favour of pembrolizumab versus the ACT was shown both for women and for men. Probability and extent in both subgroups concurred with the results in the total relevant subpopulation. In the present constellation, the results on this subgroup analysis were therefore considered as not relevant and were not considered further in the present benefit assessment. Hereinafter, only the results for the total relevant subpopulation, in which a hint of lesser harm from pembrolizumab versus the ACT was shown, are considered for this outcome.

Discontinuation due to adverse events

There was an effect modification by the characteristic "region" for the outcome "discontinuation due to AEs". Statistically significant differences in favour of pembrolizumab versus cetuximab + chemotherapy were shown both for patients from North America and for patients from Europe. For patients from the rest of the world, in contrast, no statistically significant difference was shown. The region of Europe was relevant for the present benefit assessment; the results of the other regions are therefore not considered below. This resulted in a hint of lesser harm from pembrolizumab in comparison with the ACT.

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.

Discontinuation due to adverse events

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 "discontinuation due to AEs" was assigned to the outcome category of non-serious/non-severe AEs.

The company did not assign the outcome "discontinuation due to AEs" to an outcome category.

Immune-related serious adverse events and immune-related severe adverse events (CTCAE grade ≥ 3)

By definition, only serious or severe AEs (CTCAE grade ≥ 3) are included in the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". For this reason, both outcomes were assigned to the outcome category of serious/severe AEs.

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

Further specific adverse events

There was no information available to draw conclusions on the proportions of SAEs or severe AEs (CTCAE grade ≥ 3) in the following specific outcomes: paronychia, ear and labyrinth disorders, asthenia, and dizziness. Therefore, both outcomes were 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), blood and lymphatic system disorders (CTCAE grade ≥ 3), anaemia (CTCAE grade ≥ 3), gastrointestinal disorders (CTCAE grade ≥ 3), mucosal inflammation (CTCAE grade ≥ 3), investigations (CTCAE grade ≥ 3), hypomagnesaemia (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 vs. cetuximab + chemotherapy[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. cetuximab + chemotherapy[a]** **Quantile of time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival Disease status Metastatic	Median: 13.1 vs. 9.7 HR: 0.62 [0.49; 0.79]; p < 0.001 probability: "hint"	Outcome category: mortality CI_u < 0.85 added benefit, extent: "non-quantifiable"[d]
Recurrent	Median: 11.5 vs. 12.1 HR: 1.04 [0.74; 1.45]; p = 0.835	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (EORTC QLQ-C30)	No usable data available[e]	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-H&N35)	No usable data available[e]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean (week 9): 72.5 vs. 72 MD: 0.50 [−3.07; 4.07]; p = 0.783	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 functional scales	No usable data available[e]	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-H&N35 symptom scales)	No usable data available[e]	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 21.4 vs. 10.6 HR: 0.78 [0.60; 1.02]; p = 0.067	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 5.5 vs. 0.9 HR: 0.41 [0.33; 0.51]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% lesser harm, extent: "major"
Discontinuation due to AEs Region Europe	Median: NA vs. NA HR: 0.20 [0.08; 0.48]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. cetuximab + chemotherapy[a]** **Quantile of time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Immune-related SAEs	Median: NA vs. NA HR: 1.66 [0.76; 3.61]; p = 0.204	Greater/lesser harm not proven
Immune-related severe AEs (CTCAE grade ≥ 3)	Median: NA vs. NA HR: 0.65 [0.36; 1.16]; p = 0.142	Greater/lesser harm not proven
Paronychia (PT, AEs)	Proportion of events: 0.4% vs. 12.2% RR: 0.03 [0.0 vs. 0.23]; p < 0.001 probability: "indication"[f]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Skin and subcutaneous tissue disorders (SOC, AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 0.37 [0.17; 0.77] p = 0.008 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Ear and labyrinth disorders (SOC, AEs)	Median: NA vs. NA HR: 0.44 [0.26; 0.75]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Asthenia (PT, AEs)	Proportion of events: 5.1% vs. 13.1% RR: 0.39 [0.21; 0.72]; p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Dizziness (PT, AEs)	Proportion of events: 4.7% vs. 11.8% RR: 0.40 [0.21; 0.76]; p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Blood and lymphatic system disorders (SOC, AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 0.13 [0.08; 0.23]; p < 0.001 probability: "indication"[f]	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Anaemia (PT, AEs [CTCAE grade ≥ 3])	Proportion of events: 4.7% vs. 14.7% RR: 0.32 [0.17; 0.60]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab vs. cetuximab + chemotherapy[a]** **Quantile of time to event (months) or MD** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Gastrointestinal disorders (SOC, AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 0.38 [0.22; 0.67]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Mucosal inflammation (PT; AEs [CTCAE grade ≥ 3])	Proportion of events: 1.6% vs. 5.3% RR: 0.29 [0.10; 0.89]; p = 0.022 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Investigations (SOC, AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 0.42 [0.26; 0.67]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Hypomagnesaemia (PT, AEs [CTCAE grade ≥ 3])	Proportion of events: 0% vs. 4.1% RR: 0.05 [0.00; 0.77]; p = 0.001 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SOC, AEs [CTCAE grade ≥ 3])	Median: NA vs. NA HR: 1.82 [1.02; 3.24]; HR[g]: 0.55 [0.31; 0.98] p = 0.042 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"

a. Carboplatin or cisplatin + 5-FU.
b. Probability provided if a statistically significant and relevant effect is present.
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).
d. See Sections 2.4.3 and 2.4.4 for reasons.
e. See Section 2.7.4.3.2 of the full dossier assessment for reasons.
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.
g. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

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; 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; SOC: System Organ Class; 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 in comparison with cetuximab + chemotherapy[a]

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ disease status (metastatic) hint of an added benefit – extent: “non-quantifiable”	
Side effects *Serious/severe side effects* ▪ Severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: “major”; ▫ including, each with a hint for extent: “major”: - anaemia (CTCAE grade ≥ 3) - gastrointestinal disorders (CTCAE grade ≥ 3) - investigations (CTCAE grade ≥ 3) ▫ including, each with a hint for extent: “considerable”: - skin and subcutaneous tissue disorders (CTCAE grade ≥ 3) - mucosal inflammation (CTCAE grade ≥ 3) - hypomagnesaemia (CTCAE grade ≥ 3) ▫ including, with an indication of extent: “major”: - blood and lymphatic system disorders (CTCAE grade ≥ 3) *Non-serious/non-severe side effects* ▪ Discontinuation due to AEs hint of lesser harm – extent: “considerable” ▪ Paronychia indication of lesser harm – extent: “considerable” ▪ Ear and labyrinth disorders hint of lesser harm – extent: “considerable” ▪ Asthenia hint of lesser harm – extent: “considerable” ▪ Dizziness: hint of lesser harm – extent: “considerable”	**Side effects** *Serious/severe side effects* ▪ Respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3) hint of greater harm – extent: “minor”
No usable data are available for symptoms and health-related quality of life.	
a. Carboplatin or cisplatin + 5-FU. 5-FU: 5-fluorouracil; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

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

The positive effects in overall survival were only shown in patients with metastatic disease. For this reason, the balancing of positive and negative effects below is conducted separately by disease status.

Patients with metastatic disease

Positive effects in overall survival were shown for patients with metastatic disease status. No Kaplan-Meier curves were available for the subgroups; these would be necessary for the assessment of the extent of added benefit. This is due to the intersecting course of the Kaplan-Meier curves for overall survival of the total population. Based on the data presented, it remains unclear to what extent the characteristic "disease status" is an explanatory factor for this course of the curves and thus also whether the HR presented is an adequate representation of the effect over the total observation period. For this reason, the extent of the added benefit for patients with metastatic disease is non-quantifiable.

Further positive effects in the outcome categories of serious/severe side effects and non-serious/non-severe side effects, partly with the extent "major", were shown for patients with metastatic disease. These positive effects were accompanied by greater harm with the extent "minor" in the specific AE "severe respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)". No usable results were available for the outcome category "health-related quality of life" and for symptoms.

Overall, the positive effects predominate, which are not called into question by the negative effect. In summary, there is a hint of a non-quantifiable, but (due to the advantages in the outcome category of side effects) at least considerable added benefit of pembrolizumab versus the ACT for adults with metastatic HNSCC whose tumours express PD-L1 with a CPS ≥ 1.

Patients with recurrent disease

Positive effects were shown for patients with (unresectable) recurrent disease status, but only in the outcome categories of serious/severe side effects and non-serious/non-severe side effects. As was the case for patients with metastatic disease, these positive effects were accompanied by greater harm with the extent "minor" in the specific AE "severe respiratory, thoracic and mediastinal disorders (CTCAE grade ≥ 3)". It should also be noted that no usable results were available for the outcome category "health-related quality of life" and for symptoms.

Overall, there was a hint of considerable added benefit of pembrolizumab in comparison with the ACT for patients with recurrent disease status.

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

Table 20: Pembrolizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	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[b]	**Cetuximab + carboplatin + 5-FU or cetuximab + cisplatin + 5-FU** *or* radiochemotherapy with cisplatin ± 5-FU (only for patients with locally advanced head and neck squamous cell carcinoma) *or* cisplatin + docetaxel + 5-FU as induction chemotherapy with subsequent radiotherapy/radiochemotherapy (only for patients with locally advanced head and neck squamous cell carcinoma)	
With metastatic disease status		Hint of non-quantifiable, but at least considerable added benefit[c]
With recurrent disease status		Hint of considerable added benefit[c]

a. 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**.
b. 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].
c. 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; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CPS: combined positive score; 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 considerable added benefit for the total relevant subpopulation.

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.

Merck Sharp & Dohme. A study of pembrolizumab (MK-3475) for first line treatment of recurrent or metastatic squamous cell cancer of the head and neck (MK-3475-048/KEYNOTE-048): study details [online]. In: ClinicalTrials.gov. 27.11.2019 [Accessed: 06.01.2020]. URL: https://ClinicalTrials.gov/show/NCT02358031.

Merck Sharp & Dohme. A phase 3 clinical trial of pembrolizumab (MK-3475) in first line treatment of recurrent/metastatic head and neck squamous cell carcinoma [online]. In: EU Clinical Trials Register. [Accessed: 06.01.2020]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-003698-41.

Merck Sharp & Dohme. A phase 3 clinical trial of pembrolizumab (MK-3475) in first line treatment of recurrent/mestastatic head and neck squamous cell carcinoma; study KEYNOTE 048; clinical study report [unpublished]. 2019.

Merck Sharp & Dohme Peru. A phase 3 clinical trial of pembrolizumab (MK-3475) in first line treatment of recurrent/metastatic head andneck squamous cell carcinoma [online]. In: Clinical Trials Peruvian Registry. [Accessed: 06.01.2020]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=016-15.

References for English extract

Please see full dossier assessment for full reference list.

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

1. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Pembrolizumab (neues Anwendungsgebiet: Plattenepithelkarzinom Kopf-Hals-Bereich, PD-L1-Expression ≥ 1%, Erstlinie, Monotherapie); zweckmäßige Vergleichstherapie. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/512/#zweckmaessige-vergleichstherapie].

2. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 01.07.2019]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

3. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58.

4. MSD. Keytruda 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 11.2019 [Accessed: 09.12.2019]. URL: https://www.fachinfo.de/.

5. MSD. Keytruda 50 mg/ml Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 11.2019 [Accessed: 09.12.2019]. URL: https://www.fachinfo.de/.

6. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008; 359(11): 1116-1127.

7. Merck. Erbitux 5 mg/ml Infusionslösung: Fachinformation [online]. 05.2019 [Accessed: 10.12.2019]. URL: https://www.fachinfo.de/.

8. Ribosepharm. Ribocarbo-L: Fachinformation [online]. 02.2017 [Accessed: 10.12.2019]. URL: https://www.fachinfo.de/.

9. Ribosepharm. Cisplatin-Lösung Ribosepharm: Fachinformation [online]. 12.2018 [Accessed: 10.12.2019]. URL: https://www.fachinfo.de/.

10. Bendalis. BENDA-5 FU 50 mg/ml: Fachinformation [online]. 01.2019 [Accessed: 10.12.2019]. URL: https://www.fachinfo.de/.

11. Leitlinienprogramm Onkologie. S3-Leitlinie: Diagnostik, Therapie und Nachsorge des Larynxkarzinoms; Langversion 1.1 [online]. 11.2019 [Accessed: 28.01.2020]. URL: https://www.awmf.org/uploads/tx_szleitlinien/017-076OLl_S3_Larynxkarzinom_2019-11.pdf.

12. National Comprehensive Cancer Network. NCCN clinicak guidelines in oncology (NCCN guidelines): head and neck cancers; NCCN evidence blocks; version 3.2019 [online]. 16.09.2019 [Accessed: 17.12.2019]. URL: https://www.nccn.org/professionals/physician_gls/default.aspx.

13. 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.

14. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2019/a19-100-pembrolizumab-plattenepithelkarzinom-der-kopf-hals-region-monotherapie-nutzenbewertung-gemaess-35a-sgb-v.12830.html.