IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Nivolumab (squamous cell carcinoma of the head and neck) –

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

Extract

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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
5-FU	5-fluorouracil
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-H&N35	Quality of Life Questionnaire-Head and Neck Cancer 35
RCT	randomized controlled trial
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
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 nivolumab. 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 29 May 2017.

Research question

The aim of the present report was to assess the added benefit of nivolumab as monotherapy in comparison with the appropriate comparator therapy (ACT) in adults with squamous cell carcinoma of the head and neck (SCCHN) who have progressed during or after platinum-based therapy.

For the benefit assessment of nivolumab, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT[a]**
Adults with squamous cell carcinoma of the head and neck who have progressed during or after platinum-based therapy	Individual treatment of physician's choice (chemotherapy, radiotherapy and/or surgery; in case of drug treatment under consideration of the respective approval)
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In its choice of the ACT, the company initially concurred with the G-BA's specification. However, the company then continues to explain that individual treatment of physician's choice was best represented by the 3 drug treatment options cetuximab, docetaxel and methotrexate (each as monotherapy). The company did not take into account the G-BA's provision to consider the respective approval.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. In accordance with the G-BA, the respective approval was considered for drug treatments. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Characteristics of the study and of the interventions

Study CA209-141 was used for the benefit assessment of nivolumab. This was an open-label randomized controlled trial (RCT) comparing nivolumab with a treatment of physician's choice (choice from the drug treatment options cetuximab, docetaxel and methotrexate).

Adult patients (Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 to 1) with histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV, were included in the study. Their tumour was not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Tumour progression or recurrence was detected during or within 6 months of the last dose of platinum-based chemotherapy.

A total of 361 patients were randomized in a ratio of 2:1 to 2 study arms: 240 patients to the nivolumab arm and 121 patients to the comparator arm. Before randomization, the investigator determined for patients in both study arms which treatment they would receive in case of allocation to the comparator arm (cetuximab, methotrexate or docetaxel, each as monotherapy).

Treatment with the randomized study medication was conducted until disease progression, occurrence of unacceptable side effects or withdrawal of consent. After discontinuation of the study medication, subsequent therapies could be administered. There was no limitation regarding subsequent therapy.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were symptoms, health status, health-related quality of life and adverse events (AEs).

Implementation of the appropriate comparator therapy in the study

The G-BA specified individual treatment of physician's choice as ACT. This comprised chemotherapy, radiotherapy and/or surgery; the respective approval status was to be considered in case of drug treatment. Several drug treatment options are approved in the therapeutic indication investigated.

Most drug treatment options are a combination therapy with cisplatin or carboplatin (e.g. 5-fluorouracil [5-FU] or docetaxel). According to the chosen inclusion criteria, however, the CA209-141 study was designed to investigate only patients with resistance to platinum-based therapy (due to early progression during or shortly after platinum-based therapy). Repeated platinum-based therapy is usually not indicated for this population (this also concurs with the G-BA consultation). Hence the fact that the patients included in the CA209-141 study did not have this treatment option constituted no deficiency for these patients.

In the CA209-141 study, the investigators had the choice between 3 drug treatments, each as monotherapy: cetuximab (only in countries with corresponding approval), methotrexate or

docetaxel. The company argued that, in accordance with current guidelines and the actual health care setting, these drug treatment options were the best representation of the ACT specified by the G-BA ("individual treatment of physician's choice"). However, methotrexate is the only one of these treatments to be approved as monotherapy in the therapeutic indication. Cetuximab and docetaxel are not approved as monotherapy in Germany. Since the patient group investigated in the CA209-141 study is not eligible for repeated platinum-based therapies, methotrexate is generally the only remaining approved drug treatment option for this patient group. In the consultation with the G-BA, it was also recommended to the company to use the methotrexate subpopulation of the CA209-141 study for proving the added benefit. Due to the existing approval, the company itself found methotrexate to be of particular relevance as comparator therapy and presented the results of the methotrexate subpopulation as supplementary information in Module 4 G.

Since the decision about which treatment the patients in the study were to receive had already been made for all participants before randomization, randomization was maintained also for the methotrexate subpopulation. A total of 52 patients in the comparator arm were to be treated with methotrexate. In the nivolumab arm, methotrexate treatment was planned for 119 patients in case of allocation to the comparator arm. The methotrexate subpopulation therefore contained almost half of all patients in the total population.

The ACT specified by the G-BA comprised the non-drug treatment options radiotherapy and/or surgery in addition to the drug treatments. It is unclear whether and to what extent the drug treatments in the CA209-141 study were combined with non-drug treatments. It is also unclear whether the patients included in the study would have been generally eligible also for palliative therapy alone with non-drug treatments.

In summary, the methotrexate subpopulation of the CA209-141 study was an adequate implementation of the ACT for patients with early recurrence during or after platinum-based therapy. The therapeutic indication of nivolumab also comprises patients who can be treated with repeated platinum-based therapy, however. These are patients with later progression (progression after more than 6 months after platinum-based therapy). The company presented no data for this patient group.

Analysis and data cut-offs

The dossier contained results of 2 data cut-offs. Information on frequent AEs in the relevant subpopulation was missing completely for the first data cut-off submitted by the company as supplementary information. These analyses were available for the second data cut-off primarily considered by the company; however, some specific AEs (particularly immune-related AEs) and subgroup results on specific AEs were missing. The results of the second data cut-off were used for the present assessment because of the longer observation period and because of the data availability.

Risk of bias

The risk of bias at study level was rated as low for the CA209-141 study. At outcome level, the risk of bias was rated as low for overall survival and as high for all other outcomes.

Results

Mortality

A statistically significant difference in favour of nivolumab in comparison with methotrexate was shown for the outcome "overall survival". This resulted in an indication of an added benefit of nivolumab in comparison with methotrexate.

Morbidity (symptoms and health status) and health-related quality of life

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Head and Neck Cancer 35 (QLQ-H&N35). The outcome "health status" was recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC-QLQ-C30. For all outcomes, there were no usable data for the benefit assessment due to the large proportion of patients not considered in the analyses (> 30%). The overall response rate of the questionnaires was far below 70% even at the first date of analysis after randomization. Hence there was no hint of an added benefit of nivolumab in comparison with methotrexate for the outcomes on symptoms, health status and health-related quality of life; an added benefit is therefore not proven.

Side effects

- Serious adverse events (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) and discontinuation due to AEs

There were no statistically significant differences between the treatment groups for the outcomes "severe AEs (CTCAE grade 3–4)", "SAEs" and "discontinuation due to AEs". There was an effect modification by the characteristic "region" for the outcome "severe AEs (CTCAE grade 3–4)", however. In the subgroup "Europe and rest of the world" (without North America), there was a statistically significant difference in favour of nivolumab in comparison with methotrexate; in contrast, this advantage was not shown in the region of North America. Since the subgroup "Europe and rest of the world" (without North America) includes the region relevant for the health care area (Europe), the subgroup "North America" is not considered further. Hence there was a hint of lesser harm of nivolumab in comparison with methotrexate for the region "Europe and rest of the world" (without North America).

There was no hint of greater or lesser harm from nivolumab in comparison with methotrexate for the outcomes "SAEs" and "discontinuation due to AEs"; greater or lesser harm is therefore not proven for these outcomes.

- Specific AEs

There were statistically significant differences to the disadvantage of nivolumab in comparison with methotrexate for each of the following outcomes: respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, and headache. The extent of the greater harm for the outcome "skin and subcutaneous tissue disorders" from the category of non-serious/non-severe side effects was no more than marginal. This resulted in no hint of greater or lesser harm of nivolumab in comparison with methotrexate for the outcome "skin and subcutaneous tissue disorders". In contrast, there was a hint of greater harm of nivolumab in comparison with methotrexate for the outcomes "respiratory, thoracic and mediastinal disorders" and "headache".

A statistically significant difference in favour of nivolumab in comparison with methotrexate was shown for the outcome "mucosal inflammation". This resulted in a hint of lesser harm from nivolumab in comparison with methotrexate for this outcome.

There were no data for the outcome "pneumonitis" for the relevant subpopulation. The dossier contained no suitable operationalization for immune-related AEs.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the probability and the extent of the added benefit of the drug nivolumab compared with the ACT is assessed as follows:

In the overall assessment, mostly positive and, to a lesser extent, negative effects were determined for nivolumab in comparison with methotrexate.

On the positive side, there is an indication of a considerable added benefit for the outcome "overall survival".

Regarding side effects, a hint of lesser harm of nivolumab with the extent "major" was shown for the overall rate of severe AEs (CTCAE grade 3–4). Some non-severe AEs were less common (mucosal inflammation), some were more common (respiratory, thoracic and mediastinal disorders as well as headache). Overall, there were no usable data on pneumonitis and immune-related side effects.

The data were also not usable for symptoms and health-related quality of life.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

In the overall consideration, neither the negative effects in non-serious/non-severe side effects nor the missing information on pneumonitis, on immune-related AEs and on symptoms and quality of life completely outweighed the positive effects of nivolumab particularly regarding the outcome "overall survival" and severe AEs (CTCAE grade 3–4).

In summary, there is an indication of considerable added benefit of nivolumab in comparison with methotrexate for adults with progression during or within 6 months after platinum-based therapy.

No data were available for adults with progression after more than 6 months after platinum-based therapy; an added benefit is not proven for this patient group.

Table 3 presents a summary of the probability and extent of the added benefit of nivolumab.

Table 3: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with squamous cell carcinoma of the head and neck who have progressed during or after platinum-based therapy	Individual treatment of physician's choice (chemotherapy, radiotherapy and/or surgery; in case of drug treatment under consideration of the respective approval)	▪ Patients with progression during or within 6 months after platinum-based therapy[b]: indication of considerable added benefit ▪ Patients with progression after more than 6 months after platinum-based therapy: added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: Methotrexate is usually the only remaining approved drug treatment option for this patient group. Nivolumab was investigated in comparison with methotrexate in the relevant subpopulation of the CA209-141 study. Only patients with an ECOG PS of 0 or 1 were included in the study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

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 was to assess the added benefit of nivolumab as monotherapy in comparison with the ACT in adults with SCCHN who have progressed during or after platinum-based therapy.

For the benefit assessment of nivolumab, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of nivolumab

Therapeutic indication	**ACT[a]**
Adults with squamous cell carcinoma of the head and neck who have progressed during or after platinum-based therapy	Individual treatment of physician's choice (chemotherapy, radiotherapy and/or surgery; in case of drug treatment under consideration of the respective approval)
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

In its choice of the ACT, the company initially concurred with the G-BA's specification. However, the company then continues to explain that individual treatment of physician's choice was best represented by the 3 drug treatment options cetuximab, docetaxel and methotrexate (each as monotherapy) (see also Section 2.7.1 of the full dossier assessment). The company did not take into account the G-BA's provision to consider the respective approval.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. In accordance with the G-BA, the respective approval was considered for drug treatments. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

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 nivolumab (status: 3 April 2017)
- bibliographical literature search on nivolumab (last search on 3 April 2017)
- search in trial registries for studies on nivolumab (last search on 3 April 2017)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab (last search on 8 June 2017)

The check identified no additional relevant study.

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: nivolumab vs. treatment of physician's choice

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CA209-141	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

Study CA209-141 was used for the benefit assessment of nivolumab. This corresponded to the company's approach.

For the benefit assessment, the subpopulation of patients was assessed for which the investigator had determined treatment with methotrexate before randomization (in case of allocation to the comparator arm) (methotrexate subpopulation; see next Section 2.3.2). This deviates from the approach of the company, which assessed the total population and considered the methotrexate subpopulation as supplementary information. The results of the total population of the CA209-141 study are presented in Appendix C as supplementary information.

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Characteristics of the study and of the interventions

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

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab vs. treatment of physician's choice

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CA209-141	RCT, open-label, parallel	Adults (≥ 18 years) with recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV[b], with disease progression during or within 6 months after platinum-based therapy and ECOG PS ≤ 1 without active brain metastases.	Nivolumab (N = 240) treatment of physician's choice[c] (N = 121) Relevant subpopulation thereof: nivolumab (n = 119) methotrexate (n = 52)	Screening: 28 days Treatment: until progression[d], until occurrence of unacceptable side effects or withdrawal of consent Observation: follow-up: outcome-specific, at most until death	55 study centres in Argentina, Brazil, Canada, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Spain, Switzerland, Taiwan, USA, United Kingdom 5/2014–9/2016[e]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for the present benefit assessment.
b: SCCHN not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy).
c: Before randomization, the investigator had to choose between cetuximab, methotrexate or docetaxel for patients in both study arms.
d: In the nivolumab arm, treatment beyond initial radiologically confirmed progression is allowed under certain preconditions, including the following: if the investigator considers continued treatment to have a clinical benefit for the patient; if treatment is tolerated; if the performance status remains stable. Treatment should be discontinued in case of further radiological progression.
e: The study duration depended on reaching a predefined number of events for the primary outcome "OS" (278 deaths). First planned interim analysis (12/2015): after reaching 70% (195 deaths) of deaths; second analysis (9/2016): 289 deaths were reached.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; RCT: randomized controlled trial; SCCHN: squamous cell carcinoma of the head and neck; SPC: Summary of Product Characteristics; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: nivolumab vs. treatment of physician's choice

Study	Intervention	Comparison[a]	Prior and concomitant medication
CA209-141	Nivolumab 3 mg/kg body weight as 60-minute IV infusion every 2 weeks no dose adjustment allowed[b]	Treatment of physician's choice ▪ methotrexate 40 mg/m² BSA IV weekly; escalation to 60 mg/m² BSA and reduction to 20 mg/m² BSA possible[c, d, e] ▪ *cetuximab[f] initially 400 mg/m² BSA IV, then 250 mg/m² BSA IV weekly; reduction to 150 mg/m² BSA possible* ▪ *docetaxel 30 mg/m² BSA IV weekly; escalation to 40 mg/m² BSA and reduction to 20 mg/m² BSA possible*	Pretreatment: platinum-based chemotherapy in the adjuvant, primary (as radio-chemotherapy), recurrent or metastatic setting Concomitant treatment permitted: surgery of individual lesions[g] or palliative radiotherapy in non-target lesions or lesions of the central nervous system[h] Non-permitted concomitant treatment: ▪ immunosuppressants[i] ▪ antineoplastic treatment (e.g. chemotherapy, hormonal therapy, immunotherapy) ▪ systemic corticosteroids > 10 mg daily[i, j]

a: The subpopulation of the study relevant for the present benefit assessment received treatment with methotrexate.
b: Dose delays due to AEs were allowed, without relevant deviations from the SPC [3].
c: The SPC [4] recommends a dosage of 40 to 60 mg/m², referring to recently published treatment protocols for adjustments.
d: Dose reductions in case of AEs were permitted following fixed regimens (first reduction to 30 to 40 mg/m²; second reduction to 20 to 30 mg/m²); no more than about 20% of the patients received dose reductions below 40 mg/m².
e: Dose delays due to AEs were permitted.
f: Cetuximab was only allowed to be administered in countries with approval as monotherapy in the therapeutic indication.
g: Complete resection (i.e. the resection was not limited to target lesions alone) was additionally possible from week 21. Only in patients with radiologically confirmed response it should be waited until no further tumour shrinkage was demonstrated.
h: If patients in the nivolumab arm require palliative radiotherapy, nivolumab treatment should be interrupted from at least 1 week before until at least 1 week after radiotherapy.
i: Except for treating treatment-related AEs.
j: Dexamethasone or equivalent 8 mg orally twice daily are administered as premedication on the day before the docetaxel infusion, on the day of the infusion and on the day after the infusion.
AE: adverse event; BSA: body surface area; RCT: randomized controlled trial; vs.: versus

The CA209-141 study was a randomized, open-label, controlled study.

Adult patients (ECOG PS of 0 to 1) with histologically confirmed recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), stage III/IV, were included in the study. Their tumour was not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Patients with carcinoma with primary location in the nasopharynx or the salivary gland and patients with active brain metastases were excluded. Tumour

progression or recurrence was detected during or within 6 months of the last dose of platinum-based chemotherapy. This platinum-based therapy could be conducted in the adjuvant, primary (in each case as radiochemotherapy), recurrent or metastatic setting.

According to the chosen inclusion criteria, the study was designed to investigate patients in good general condition who had already progressed during or within 6 months after platinum-based therapy (i.e. patients who, in general, are resistant to platinum-based therapy). Due to protocol violation, the study also investigated patients with later progression (progression after more than 6 months after platinum-based therapy), but only to a very small extent (no more than 7.5% in the nivolumab arm and 3.3% in the comparator arm).

A total of 361 patients were randomized in a ratio of 2:1 to 2 study arms: 240 patients to the nivolumab arm and 121 patients to the comparator arm. Before randomization, the investigator determined for patients in both study arms which treatment they would receive in case of allocation to the comparator arm (cetuximab, methotrexate or docetaxel, each as monotherapy). Treatment with cetuximab was only allowed in countries where this drug is approved as monotherapy. Patients were stratified by prior cetuximab treatment.

The patients in the nivolumab arm were treated without relevant deviations from the Summary of Product Characteristics (SPC) [3]. Patients in the comparator arm weekly received 1 of 3 treatment options chosen by the investigator: cetuximab, methotrexate or docetaxel. Of these 3 comparator therapies, only treatment with methotrexate is relevant for the present benefit assessment because of the existing approval (see also Section 2.3.2 below). Treatment with methotrexate was also in compliance with the approval [4] (see Table 7).

Treatment with the randomized study medication was conducted until disease progression, occurrence of unacceptable side effects or withdrawal of consent. Occurrence of disease progression was determined by means of the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. Under certain preconditions, patients in the nivolumab arm could receive their randomized study medication beyond radiologically confirmed disease progression (see Table 6).

After discontinuation of the study medication (e.g. due to disease progression), subsequent drug and non-drug treatments could be conducted. The dossier only contains summarizing information about concomitant and subsequent treatments. There is no detailed information as to whether these treatments were administered as concomitant or subsequent treatments. Most of the antineoplastic drug treatments mentioned in the dossier as subsequent treatments were presumably subsequent treatments after discontinuation of the study medication (because if they were concomitant treatments, they would be protocol violations). In the relevant methotrexate subpopulation, 37.8% of the patients in the nivolumab arm received such subsequent systemic treatment, and 34.6% in the methotrexate arm.

No explicit provision was made in the study design for patients to switch treatment from the comparator arm to subsequent treatment with nivolumab. Nonetheless, a small number of patients in the comparator arm received nivolumab (1.9%) after discontinuing methotrexate treatment. In the nivolumab arm, 13.4% of the patients received treatment with methotrexate in the framework of the subsequent therapeutic strategy.

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were symptoms, health status, health-related quality of life and AEs.

Implementation of the appropriate comparator therapy in the study

The G-BA specified individual treatment of physician's choice as ACT. This comprised chemotherapy, radiotherapy and/or surgery; the respective approval status was to be considered in case of drug treatment. Several drug treatment options are approved in the therapeutic indication investigated.

Most drug treatment options are a combination therapy with cisplatin or carboplatin (e.g. 5-FU [5] or docetaxel [6]). According to the chosen inclusion criteria, however, the CA209-141 study was designed to investigate only patients with resistance to platinum-based therapy (due to early progression during or shortly after platinum-based therapy). Repeated platinum-based therapy is usually not indicated for this population (this also concurs with the G-BA consultation [7]). Hence the fact that the patients included in the CA209-141 study did not have this treatment option constituted no deficiency for these patients.

In the CA209-141 study, the investigators had the choice between 3 drug treatments, each as monotherapy: cetuximab (only in countries with corresponding approval), methotrexate or docetaxel. The company argued that, in accordance with current guidelines and the actual health care setting, these drug treatment options were the best representation of the ACT specified by the G-BA ("individual treatment of physician's choice") (see also Section 2.7.1 of the full dossier assessment). However, methotrexate is the only one of these treatments to be approved as monotherapy in the therapeutic indication [4]. Cetuximab [8] and docetaxel [6] are not approved as monotherapy in Germany. Since the patient group investigated in the CA209-141 study is not eligible for repeated platinum-based therapies, methotrexate is generally the only remaining approved drug treatment option for this patient group. In the consultation with the G-BA [7], it was also recommended to the company to use the methotrexate subpopulation of the CA209-141 study for proving the added benefit. Due to the existing approval, the company itself found methotrexate to be of particular relevance as comparator therapy and presented the results of the methotrexate subpopulation as supplementary information in Module 4 G.

Since the decision about which treatment the patients in the study were to receive had already been made for all participants before randomization, randomization was maintained also for the methotrexate subpopulation. A total of 52 patients in the comparator arm were to be treated with methotrexate. In the nivolumab arm, methotrexate treatment was planned for

119 patients in case of allocation to the comparator arm. The methotrexate subpopulation therefore contained almost half of all patients in the total population.

The ACT specified by the G-BA comprised the non-drug treatment options radiotherapy and/or surgery in addition to the drug treatments. It is unclear whether and to what extent the drug treatments in the CA209-141 study were combined with non-drug treatments. It is also unclear whether the patients included in the study would have been generally eligible also for palliative therapy alone with non-drug treatments (see Section 2.7.2.4.1 of the full dossier assessment).

In summary, the methotrexate subpopulation of the CA209-141 study was an adequate implementation of the ACT for patients with early recurrence during or after platinum-based therapy. The therapeutic indication of nivolumab also comprises patients who can be treated with repeated platinum-based therapy, however. These are patients with later progression (progression after more than 6 months after platinum-based therapy). The company presented no data for this patient group.

Treatment duration and follow-up observation

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

Table 8: Planned duration of follow-up – RCT, direct comparison: nivolumab vs. methotrexate

Study **Outcome category** **Outcome**	**Planned follow-up**
CA209-141	
Mortality	
overall survival	▪ first follow-up visit[a] ▪ second follow-up visit[b] ▪ then every 3 months until death or end of study participation
Morbidity	
symptoms (EORTC QLQ-H&N35 and EORTC QLQ-C30)	▪ first follow-up visit[a] ▪ second follow-up visit[b]
health status (EQ-5D VAS)	▪ first follow-up visit[a] ▪ second follow-up visit[b] ▪ then every 3 months until death or end of study participation
Health-related quality of life (EORTC QLQ-C30)	▪ first follow-up visit[a] ▪ second follow-up visit[b]
Side effects	
all outcomes in the category "side effects"[c]	▪ 30 days after the last dose of the study medication[d] ▪ 100 days after the last dose of the study medication[d]

a: 35 days after the last dose of the study medication or, in dose delays, on the day of treatment discontinuation (if due to dose delay the date of the treatment discontinuation was already > 35 days after the last dose of the study medication).
b: 80 days after the first follow-up visit.
c: Drug-related side effects were additionally documented beyond the second follow-up visit.
d: Information according to SAP and CSR; the study protocol contains discrepant information (where both follow-up visits[a, b] are named also for side effects).
CSR: clinical study report; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire Core-30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Only overall survival and health status were to be recorded until the end of study participation.

The observation periods for the outcomes "side effects", "symptoms" and "health-related quality of life" were systematically shortened because they were only documented for the time period of treatment (plus a short follow-up period). 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 survival and health status.

Analysis and data cut-offs

Overall survival was the primary outcome of the study. Patient-relevant secondary outcomes were symptoms, health status, health-related quality of life and AEs.

An interim analysis was planned for the time point of reaching 70% (195 deaths) of the deaths required for the final analysis. This data cut-off was conducted on 18 December 2015 and is referred to as "first data cut-off" in the present benefit assessment. Following a recommendation by the independent Data Monitoring Committee, the study was stopped prematurely at this time point because the superiority of nivolumab for overall survival was shown.

With 289 deaths at the second analysis (20 September 2016), the number of 278 deaths mandated in the study protocol for the final analysis was reached. This data cut-off is referred to as "second data cut-off".

The company presented results of both data cut-offs for all outcomes both for the methotrexate subpopulation and for the total population. Information on frequent AEs in the relevant subpopulation was missing completely for the first data cut-off submitted by the company as supplementary information. These analyses were available for the second data cut-off primarily considered by the company; however, some specific AEs (particularly immune-related AEs) and subgroup results on specific AEs were missing.

The results of the second data cut-off (20 September 2016) were used for the present assessment because of the longer observation period and because of the data availability. This concurs with the company's approach.

Characteristics of the study population

The characteristics of the relevant subpopulation are shown in Table 9.

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab vs. methotrexate

Study Characteristics Category	**Nivolumab**	**Methotrexate**
CA209-141	N[a] = 119	N[a] = 52
Age [years], mean (SD)	59.5 (9.7)	59.8 (11.8)
Sex [F/M], %	19.3/80.7	15.4/84.6
Region n (%)		
North America	47 (39.5)	19 (36.5)
Europe	58 (48.7)	25 (48.1)
Rest of the world	14 (11.8)	8 (15.4)
Ethnicity n (%)		
White	97 (81.5)	41 (78.8)
Black/African American	3 (2.5)	2 (3.8)
Asian	16 (13.4)	9 (17.3)
Other	3 (2.5)	0
ECOG Performance Status n (%)		
0	23 (19.3)	6 (11.5)
1	94 (79.0)	44 (84.6)
≥ 2	1 (0.8)	1 (1.9)
Unknown	1 (0.8)	1 (1.9)
Location of primary tumour n (%)		
Oral cavity	53 (44.5)	31 (59.6)
Pharynx	49 (41.2)	11 (21.2)
Larynx	14 (11.8)	8 (15.4)
Other	3 (2.5)	2 (3.8)
Disease stage n (%)		
III	16 (13.4)	4 (7.7)
IV	102 (85.7)	48 (92.3)
Unknown	1 (0.8)	0
Smoker n (%)		
Never	19 (16.0)	15 (28.8)
Former/current	95 (79.8)	35 (67.3)
Unknown	5 (4.2)	2 (3.8)
Prior surgery n (%)		
Yes	101 (84.9)	47 (90.4)
No	18 (15.1)	5 (9.6)
Prior radiotherapy n (%)		
Yes	105 (88.2)	49 (94.2)
No	14 (11.8)	3 (5.8)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab vs. methotrexate (continued)

Study Characteristics Category	**Nivolumab**	**Methotrexate**
CA209-141	N[a] = 119	N[a] = 52
Prior cetuximab treatment according to CRF		
Yes	92 (77.3)	39 (75.0)
No	27 (22.7)	13 (25.0)
Number of prior systemic therapies n (%)		
1	42 (35.3)	21 (40.4)
2	37 (31.1)	19 (36.5)
≥ 3	40 (33.6)	12 (23.1)
Number of prior chemotherapies in the metastatic setting n (%)		
0	51 (42.9)	21 (40.4)
1	38 (31.9)	18 (34.6)
2	21 (17.6)	5 (9.6)
≥ 3	9 (7.6)	8 (15.4)
Prior systemic therapy regimen setting		
Adjuvant	ND	ND
Neo-adjuvant	ND	ND
Primary	ND	ND
Metastatic RCC	ND	ND
Treatment discontinuation[b], n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Patients who did not receive any study medication: nivolumab arm n = 3 (2.5%), comparator arm n = 6 (11.6%).
CRF: case report form; ECOG PS: Eastern Cooperative Oncology Group; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patients in the relevant subpopulation in both treatment groups of the CA209-141 study were largely comparable. Their mean age was 60 years; most patients were male and of white ethnicity. Overall, the patient population included in the study was very heterogeneous regarding disease characteristics and pretreatment. In about half of the patients, the primary tumour was located in the oral cavity. Moreover, about 2 thirds of the patients had already received 2 or more systemic treatments; about 40% had not received chemotherapy in a metastatic setting. Most patients had disease stage IV and had already received radiation and/or surgery. Information on the prior systemic therapy regimen setting was only available for the total population (presented in Appendix C, Table 22, of the full dossier assessment).

For the relevant subpopulation, there was no information on the number of patients who discontinued treatment. In the total population, 93% of the patients in the nivolumab arm and 99% of the patients in the comparator harm had already discontinued treatment at the time point of the second data cut-off. Treatment discontinuations in both arms were mostly due to progression of the disease. Information on the number of patients who discontinued the study was only available for the total population (see Table 22 of the full dossier assessment).

Course of the study

Table 10 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes for the relevant subpopulation. The information for the total population is presented as additional information in Appendix C, Table 23, of the full dossier assessment.

Table 10: Information on the course of the study – RCT, direct comparison: nivolumab vs. methotrexate (second data cut-off)

Study **Duration of the study phase** **Outcome category**	**Nivolumab**	**Methotrexate**
CA209-141	N = 116[a]	N = 46[a]
Treatment duration [months]		
Median [min; max]	1.87 [0.0; 23.5]	1.64 [0.0; 6.4]
Mean (SD)	3.82 (4.44)	2.01 (1.63)
Observation period [months]		
Overall survival		
Median [min; max]	7.18 [0.2; 23.6]	4.63 [0.4; 17.9]
Mean (SD)	8.03 (6.25)	5.94 (4.42)
Morbidity	ND	
Health-related quality of life	ND	
Side effects	ND	

a: Patients with at least 1 dose of the study medication.

max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Whereas the median treatment duration for the relevant subpopulation in the CA209-141 study was comparable in the nivolumab arm and in the methotrexate arm, the mean value showed notable differences. The mean treatment duration in the nivolumab arm (3.8 months) was almost twice as long as in the comparator arm (2.0 months). These values show that there was a different distribution of treatment durations in both treatment arms. The exact information on the reasons for treatment discontinuation was only available for the total population, however (see Appendix C, Table 22, of the full dossier assessment).

The dossier contained no information on observation periods for outcomes on morbidity, quality of life and side effects. It is not assumed, however, that there was a relevant difference between the observation periods of these outcomes because observation was only to be conducted for a few weeks after the end of treatment.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: nivolumab vs. methotrexate

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
CA209-141	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the relevant subpopulation of the study. This corresponds to the company's assessment. Limitations resulting from the open-label study design are described in Section 2.4.2 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 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-H&N35
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade 3–4)
  - pneumonitis
  - immune-related AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in Module 4 G (see Section 2.7.2.4.3 of the full dossier assessment). In contrast, the company did not present specific AEs.

Table 12 shows for which outcomes data were available in the CA209-141 study included.

Table 12: Matrix of outcomes – RCT, direct comparison: nivolumab vs. methotrexate

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-H&N35)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-LC30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Respiratory, thoracic and mediastinal disorders (AE)	Mucosal inflammation (AE)	Headache (AE)	Skin and subcutaneous tissue disorders (AE)	Pneumonitis	Immune-related AEs
CA209-141	Yes	No[a]	No[a]	No[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[b]	No[b]

a: No usable data available; proportion of patients not considered in the analysis was too large (> 30%).
b: No data for the relevant subpopulation.

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; QLQ-C30: Quality of Life Questionnaire-Core 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

2.4.2 Risk of bias

Table 13 shows the risk of bias for the relevant outcomes.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: nivolumab vs. methotrexate

Study	Study level	Outcomes												
		Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-H&N35)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-LC30)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Respiratory, thoracic and mediastinal disorders (AE)	Mucosal inflammation (AE)	Headache (AE)	Skin and subcutaneous tissue disorders (AE)	Pneumonitis	Immune-related AEs
CA209-141	L	L	–[a]	–[a]	–[a]	H[b, c]	H[b, d, e]	H[b, c]	H[b, d, e]	H[b, d, e]	H[b, d, e]	H[b, d, e]	–[f]	–[f]

a: No usable data available; proportion of patients not considered in the analysis was too large (> 30%) (see Section 2.7.2.4.3 of the full dossier assessment).
b: Large difference between the treatment groups (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis.
c: Large proportion with incomplete observation.
d: Large difference in mean treatment duration (and hence observation period) between the nivolumab arm (3.82 months) and the methotrexate arm (2.01 months).
e: Lack of blinding in subjective recording of outcomes.
f: No data available.

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; QLQ-C30: Quality of Life Questionnaire-Core 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 risk of bias for the outcome "overall survival" was rated as low in the relevant subpopulation. This concurs with the company's assessment.

The risk of bias for the relevant subpopulation for all outcomes on side effects was high because of the large difference between the treatment groups regarding the proportion of patients who were not considered in the analysis (> 5 percentage points). Further aspects resulted in an outcome-specific high risk of bias.

The company rated the risk of bias as low for the outcomes "SAEs" and "severe AEs" (CTCAE grade 3–4). It rated the risk of bias as high for the outcome "discontinuation due to AEs" only due to the lack of blinding. The company did not present specific AEs in Module 4 G and hence did not address their risk of bias.

No data were available for morbidity, quality of life, pneumonitis and immune-related side effects for the relevant subpopulation, or the data were not usable. The risk of bias for these

outcomes was therefore not assessed. The company rated the risk of bias as high for the outcomes on morbidity and quality of life because of the lack of blinding and the inadequate implementation of the intention-to-treat principle.

See Section 2.7.2.4.2 of the full dossier assessment for a detailed description of the risk of bias.

2.4.3 Results

Table 14 summarizes the results for the comparison of nivolumab with methotrexate in adults with SCCHN who have progressed during or after platinum-based therapy. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. In cases where no events occurred in a treatment arm, the effect estimation and the corresponding confidence interval for binary data were calculated by the Institute with a continuity correction of 0.5 in both treatment arms. Kaplan-Meier curves on the outcomes included, except for the specific outcomes – are available for the methotrexate subpopulation (Appendix A of the full dossier assessment).

The results for the total population are presented as supplementary information in Appendix C of the full dossier assessment.

Table 14: Results – RCT, direct comparison: nivolumab vs. methotrexate

Study Outcome category	Nivolumab		Methotrexate		Nivolumab vs. methotrexate
Outcome	**N**	**Median survival time in months [95% CI] Patients with event n (%)**	**N**	**Median survival time in months [95% CI] Patients with event n (%)**	**HR [95% CI][a]; p-value[b]**
Study CA209-141					
Mortality					
Overall survival	119	7.49 [4.83; 8.77] 94 (79.0)	52	4.40 [3.38; 5.82] 48 (92.3)	0.62 [0.44; 0.89]; 0.008
Morbidity					
Symptoms (EORTC QLQ-C30 and H&N35)			No usable data[c]		
Health status (EQ-5D VAS)			No usable data[c]		
Health-related quality of life					
EORTC QLQ-C30			No usable data[c]		
Adverse events[d]					
AEs (supplementary information)	116	0.26 [0.16; 0.39] 113 (97.4)	46	0.18 [0.07; 0.26] 43 (93.5)	–
SAEs	116	6.70 [3.25; 12.19] 57 (49.1)	46	4.70 [2.14; NC] 22 (47.8)	0.86 [0.52; 1.42]; 0.542
Severe AEs (CTCAE grade 3–4)	116	3.02 [1.97; 4.40] 72 (62.1)	46	1.87 [0.89; 3.32] 30 (65.2)	0.74 [0.48; 1.14]; 0.165
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[e]**
Discontinuation due to AEs	116	14 (12.1)	46	8 (17.4)	0.69 [0.31; 1.54]; 0.460
Specific AEs[f]					
Respiratory, thoracic and mediastinal disorders (AE)	116	54 (46.6)	46	10 (21.7)	2.14 [1.20; 3.83]; 0.004
Mucosal inflammation (AE)	116	5 (4.3)	46	8 (17.4)	0.25 [0.09; 0.72]; 0.007
Skin and subcutaneous tissue disorders (AE)	116	34 (29.3)	46	6 (13.0)	2.25 [1.01; 4.99]; 0.031

(continued)

Table 14: Results – RCT, direct comparison: nivolumab vs. methotrexate (continued)

Study Outcome category	Nivolumab		Methotrexate		Nivolumab vs. methotrexate
Outcome	**N**	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[e]**
Study CA209-141					
Headache (AE)	116	12 (10.3)	46	0	–[g]; 0.025
Pneumonitis	No data available				
Immune-related AEs	No usable data[h]				

a: Unstratified Cox model.
b: Unstratified log-rank test.
c: No usable data available; proportion of patients not considered in the analysis was too large (> 30%) (see Section 2.7.2.4.3 of the full dossier assessment).
d: AEs up to 100 days after the end of treatment except treatment discontinuation due to AEs (up to 30 days after the end of treatment), without recording of progression of the underlying disease.
e: Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test [CSZ method according to [9]).
f: AEs until 30 days after the end of treatment.
g: Effect estimate and 95% CI not meaningfully interpretable.
h: No patient-relevant operationalization (see Section 2.7.2.4.3 of the full dossier assessment).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; 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; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be derived for the outcome "overall survival", and at most hints for the outcomes of the category of side effects due to the high risk of bias.

The company assessed the added benefit of nivolumab on the basis of the total population of the CA209-141 study. The company presented the results for the relevant methotrexate subpopulation as supplementary information in Module 4 G. It considered the results in these 2 populations to be consistent. The company's assessment regarding the consistency of the results was not shared. The extent of the deviation between the assessment of the outcomes in the present benefit assessment (on the basis of the relevant subpopulation) and the assessment of the total population is summarized in Section 2.7.2.4.1 of the full dossier assessment.

Mortality

Overall survival

A statistically significant difference in favour of nivolumab in comparison with methotrexate was shown for the outcome "overall survival". This resulted in an indication of an added benefit of nivolumab in comparison with methotrexate.

Morbidity

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

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-H&N35. For both instruments, there were no usable data for the benefit assessment due to the very large proportion of patients not considered in the analyses (> 30%) (see Section 2.7.2.4.3 of the full dossier assessment). Hence there was no hint of an added benefit of nivolumab in comparison with methotrexate for the symptom outcomes; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

The outcome "health status" was recorded with the EQ-5D VAS. There were no usable data due to the very large proportion of patients not considered in the analyses (> 30%) (see Section 2.7.2.4.3 of the full dossier assessment). Hence there was no hint of an added benefit of nivolumab in comparison with methotrexate for this outcome; an added benefit is therefore not proven.

Health-related quality of life (EORTC QLQ-C30)

Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC-QLQ-C30. For the outcome "health-related quality of life", there were no usable data for the benefit assessment due to the very large proportion of patients not considered in the analyses (> 30%). Hence there was no hint of an added benefit of nivolumab in comparison with methotrexate for this outcome; an added benefit is therefore not proven.

Side effects

Serious adverse events, severe adverse events (CTCAE grade 3–4) and discontinuation due to adverse events

Analyses presented by the company excluding progression events were used for the outcomes "SAEs", "severe AEs (CTCAE grade 3–4)", and "discontinuation due to AEs" (see Section 2.7.2.4.3 of the full dossier assessment). Follow-up observation was 100 days for severe AEs (CTCAE grade 3–4) and SAEs, and 30 days for the outcome "discontinuation due to AEs".

There were no statistically significant differences between the treatment groups for the outcomes "severe AEs (CTCAE grade 3–4)", "SAEs" and "discontinuation due to AEs". There was an effect modification by the characteristic "region" for the outcome "severe AEs (CTCAE grade 3–4)", however (see Section 2.4.4). There was a hint of lesser harm of

nivolumab in comparison with methotrexate for the region "Europe and rest of the world" (without North America). For North America, there was no hint of greater or lesser harm of nivolumab in comparison with methotrexate. Since the subgroup "Europe and rest of the world" (without North America) includes the region relevant for the health care area (Europe), the subgroup "North America" is not considered further.

There was no hint of greater or lesser harm from nivolumab in comparison with methotrexate for the outcomes "SAEs" and "discontinuation due to AEs"; greater or lesser harm is therefore not proven for these outcomes.

Specific adverse events

There were statistically significant differences to the disadvantage of nivolumab in comparison with methotrexate for each of the following outcomes: respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, and headache. The extent of the greater harm of nivolumab for the outcome "skin and subcutaneous tissue disorders" from the category of non-serious/non-severe side effects was no more than marginal (see Section 2.5.1). This resulted in no hint of greater or lesser harm from nivolumab in comparison with methotrexate for this outcome. In contrast, there was a hint of greater harm of nivolumab in comparison with methotrexate for the outcomes "respiratory, thoracic and mediastinal disorders" and "headache".

A statistically significant difference in favour of nivolumab in comparison with methotrexate was shown for the outcome "mucosal inflammation". This resulted in a hint of lesser harm from nivolumab in comparison with methotrexate for this outcome.

There were no data for the outcome "pneumonitis" for the relevant subpopulation. The dossier contained no suitable operationalization for immune-related AEs (see Section 2.7.2.4.3 of the full dossier assessment).

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- region (North America, Europe, rest of the world)
- disease stage (III, IV)
- location of primary tumour (oral cavity, pharynx, larynx, other)
- prior cetuximab treatment (yes/no)

In Module 4 G, the company presented subgroup analyses for most outcomes also for the methotrexate subpopulation presented by the company as supplementary information, but

subgroup analyses on specific AEs were missing. It therefore remains unclear whether there were effect modifications for specific AEs in the subpopulation. Subgroup analyses on specific AEs were also missing for the total population.

Hereinafter, only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least 1 subgroup.

The subgroup results of nivolumab in comparison with methotrexate are summarized in Table 15.

Table 15: Subgroups (side effects) – RCT, direct comparison: nivolumab vs. methotrexate

Study	**Nivolumab**		**Methotrexate**		**Nivolumab vs. methotrexate**	
Outcome **Characteristic** **Subgroup**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]**	**p-value[a]**
CA209-141						
Severe AEs (CTCAE grade 3–4[b])						
Region						
North America	*45*	*1.61 [0.89; 9.99]* *29 (64.4)*	*14*	*NA [0.26; NC]* *4 (28.6)*	*2.34 [0.82; 6.70]*	*0.101*
Europe	*57*	*2.79 [1.84; 10.15]* *33 (57.9)*	*24*	*1.31 [0.49; 2.07]* *20 (83.3)*	*0.40 [0.22; 0.72]*	*0.002*
Rest of the world	*14*	*4.40 [2.37; 13.40]* *10 (71.4)*	*8*	*2.50 [0.53; NC]* *6 (75.0)*	*0.33 [0.10; 1.11]*	*0.064*
Total					*Interaction[c]:*	*0.010*
Region						
North America	45	1.61 [0.89; 9.99] 29 (64.4)	14	NA [0.26; NC] 4 (28.6)	2.34 [0.82; 6.70]	0.101
Europe and rest of the world	71	ND	32	ND	0.39 [0.23; 0.66]	p < 0.001[d]
					Interaction[e]:	0.003

a: Unstratified Cox model and unstratified log-rank test.
b: AEs until 100 days after the end of treatment without recording of progression of the underlying disease.
c: Unstratified Cox model with treatment, subgroup characteristic and the interaction term treatment*subgroup characteristic.
d: Institute's calculation; meta-analysis with fixed effect.
e: Institute's calculation, Cochran's Q test.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Side effects

Severe adverse events (CTCAE grade 3–4)

An effect modification (interaction test: p = 0.010) by the characteristic "region" (with the subgroups North America, Europe, rest of the world) was shown for the outcome "severe AEs (CTCAE grade 3–4)" in the CA209-141 study. In the present data situation, the subgroups with homogeneous effects (Europe and rest of the world) were aggregated to a model with fixed effect due to the identical study (see Figure 7 in Appendix B of the full dossier assessment). The interaction test between the subgroup results from the characteristic "region" (subgroup of North America, aggregated subgroup of Europe and rest of the world) resulted in a p-value of 0.003.

A statistically significant difference in favour of nivolumab was shown for the aggregated subgroup of Europe and rest of the world. This resulted in a hint of lesser harm from nivolumab in comparison with methotrexate. There was no statistically significant difference between the treatment arms for the region "North America". The subgroup "Europe and rest of the world" includes the region relevant for the health care area (Europe); the subgroup "North America" is not considered further in the assessment.

2.5 Probability and extent of added benefit

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

The approach for deriving an overall conclusion on 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 added benefit at outcome level

The present assessment was conducted for nivolumab in adults with SCCHN who have progressed during or after platinum-based therapy.

Only data of patients with resistance to platinum-based therapy were available for the assessment. These are (according to the inclusion criteria of the study) patients with early progression (during or within 6 months) after platinum-based therapy. Since, in general, methotrexate is the only remaining approved drug treatment option for this patient group, the methotrexate subpopulation of the relevant study was used for the benefit assessment.

For this patient group, the data presented in Section 2.4 resulted in the following assessments of nivolumab in comparison with methotrexate:

- an indication of an added benefit for the outcome "overall survival"

- a hint of lesser harm for the outcome “severe AEs (CTCAE grade 3–4)” in the region “Europe and rest of the world” (without North America)
- a hint of lesser harm for the outcome “mucosal inflammation”
- a hint of greater harm for each of the outcomes “respiratory, thoracic and mediastinal disorders” and “headache”

The proportion of SAEs was below 50% for each of the outcomes “respiratory, thoracic and mediastinal disorders” and “headache”. They were therefore allocated to the outcome category of non-serious/non-severe side effects.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

Table 16: Extent of added benefit at outcome level: nivolumab vs. methotrexate

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. methotrexate median time to event or proportion of events effect estimate [95% CI]; p-value probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 7.5 vs. 4.4 months HR: 0.62 [0.44; 0.89]; p = 0.008 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms		
EORTC QLQ-C30 and EORTC QLQ-H&N35 (symptom scales)	No usable data available	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data available	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (functional scales)	No usable data available	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 6.7 vs. 4.7 months HR: 0.86 [0.52; 1.42]; p = 0.542	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)[c]	Median: ND vs. ND HR: 0.39 [0.23; 0.66]; 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	Proportion of events: 12.1% vs. 17.4% RR: 0.69 [0.31; 1.54]; p = 0.460	Greater/lesser harm not proven
Specific AEs		
Respiratory, thoracic and mediastinal disorders	Proportion of events: 46.6% vs. 21.7% RR: 2.14 [1.20; 3.83] RR: 0.47 [0.26; 0.83][d] p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Mucosal inflammation	Proportion of events: 4.3% vs. 17.4% RR: 0.25 [0.09; 0.72]; p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Skin and subcutaneous tissue disorders	Proportion of events: 29.3% vs. 13.0% RR: 2.25 [1.01; 4.99] RR: 0.44 [0.20; 0.99][d] p = 0.031	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[e]

(continued)

Table 16: Extent of added benefit at outcome level: nivolumab vs. methotrexate (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab vs. methotrexate median time to event or proportion of events effect estimate [95% CI]; p-value probability**[a]	**Derivation of extent**[b]
Headache	Proportion of events: 10.3% vs. 0% RR: NC[f] p = 0.025 probability: "hint"	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"
Pneumonitis	No data available	Greater/lesser harm not proven
Immune-related AEs	No usable data available	Greater/lesser harm not proven

a: Probability provided if a statistically significant and relevant effect is present
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Results for Europe and rest of the world (without North America).
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f: Effect estimate and CI not meaningfully interpretable.

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; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of nivolumab in comparison with methotrexate

Positive effects	**Negative effects**
Mortality ▪ overall survival ▫ indication of an added benefit – extent: "considerable"	–
Serious/severe side effects ▪ severe AEs (CTCAE grade 3–4): hint of lesser harm – extent: "major"	–
Non-serious/non-severe side effects ▪ mucosal inflammation: hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ respiratory, thoracic and mediastinal disorders: indication of greater harm – extent: "minor" ▪ headache: hint of greater harm – extent: "non-quantifiable"
No results or no usable results are available for symptoms, health-related quality of life and individual specific AEs (pneumonitis and immune-related side effects).	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

In the overall assessment, mostly positive and, to a lesser extent, negative effects were determined for nivolumab in comparison with methotrexate.

On the positive side, there is an indication of a considerable added benefit for the outcome "overall survival".

Regarding side effects, a hint of lesser harm of nivolumab with the extent "major" was shown for the overall rate of severe AEs (CTCAE grade 3–4). Some non-severe AEs were less common (mucosal inflammation), some were more common (respiratory, thoracic and mediastinal disorders as well as headache). Overall, there were no usable data on pneumonitis and immune-related side effects.

The data were also not usable for symptoms and health-related quality of life.

In the overall consideration, neither the negative effects in non-serious/non-severe side effects nor the missing information on pneumonitis, on immune-related AEs and on symptoms and quality of life completely outweighed the positive effects of nivolumab particularly regarding the outcome "overall survival" and severe AEs (CTCAE grade 3–4).

In summary, there is an indication of considerable added benefit of nivolumab in comparison with methotrexate for adults with progression during or within 6 months after platinum-based therapy.

No data were available for adults with progression after more than 6 months after platinum-based therapy; an added benefit is not proven for this patient group.

The result of the assessment of the added benefit of nivolumab in comparison with the ACT is summarized in Table 18.

Table 18: Nivolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with squamous cell carcinoma of the head and neck who have progressed during or after platinum-based therapy	Individual treatment of physician's choice (chemotherapy, radiotherapy and/or surgery; in case of drug treatment under consideration of the respective approval)	▪ Patients with progression during or within 6 months after platinum-based therapy[b]: indication of considerable added benefit ▪ Patients with progression after more than 6 months after platinum-based therapy: added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. b: Methotrexate is usually the only remaining approved drug treatment option for this patient group. Nivolumab was investigated in comparison with methotrexate in the relevant subpopulation of the CA209-141 study. Only patients with an ECOG PS of 0 or 1 were included in the study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

For patients with progression during or within 6 months after platinum-based therapy, the assessment described above concurs with that of the company. The company, however, derived this added benefit on the basis of the total population. The company drew no separate conclusion on the added benefit for the patient group with progression after more than 6 months after platinum-based therapy.

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

CA209-141

Bristol-Myers Squibb. An open label, randomized phase 3 clinical trial of nivolumab vs therapy of investigator's choice in recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN): study CA209141; final clinical study report [unpublished]. 2016.

Bristol-Myers Squibb. An open label, randomized phase 3 clinical trial of nivolumab vs therapy of investigator's choice in recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCHN): study CA209141; addendum 01 to the final clinical study report [unpublished]. 2016.

Bristol-Myers Squibb. An open label, randomized phase 3 clinical trial of nivolumab vs therapy of investigator's choice in recurrent or metastatic platinum-refractory squamous cell carcinoma of the head and neck (SCCH) [online]. In: EU Clinical Trials Register. [Accessed: 14.06.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-003622-86.

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Please see full dossier assessment for full reference list.

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

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