IQWiG Reports – Commission No. A19-31

Pembrolizumab (squamous NSCLC, combination chemotherapy) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pembrolizumab (plattenepitheliales NSCLC, Kombinationschemotherapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 June 2019). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC	European Organization for Research and Treatment of Cancer
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire – Lung Cancer 13
EQ-5D	European Quality of Life-5 Dimension
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	non-small cell lung cancer
PD-L1	programmed death ligand-1
PFS	progression-free survival
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	system organ class
SPC	Summary of Product Characteristics
TPC	Treatment of Physician’s Choice
TPS	Tumor 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 in combination with carboplatin and either paclitaxel or nab-paclitaxel. 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 March 2019.

Research question

The aim of the present report was to assess the added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with the ACT for the first-line treatment of adults with metastatic squamous non-small cell lung cancer (NSCLC).

The research questions presented in Table 2 resulted from the appropriate comparator therapy (ACT) specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel

Research question	**Subindication**	**ACT[a]**
1	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression < 50%	Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel) *or* **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or **paclitaxel**; see also Appendix VI to Section K of the pharmaceutical directive) *or* **carboplatin in combination with nab-paclitaxel**
2	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression ≥50%	Pembrolizumab as monotherapy

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: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to the IASLC and the UICC), without medical indication for definitive local therapy.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; UICC: Union for International Cancer Control

The company followed the G-BA's specification on the ACT for both research questions. For research question 1, the company chose carboplatin in combination with either paclitaxel or nab-paclitaxel from the options presented.

Unless otherwise stated, carboplatin-based chemotherapy in combination with either paclitaxel or nab-paclitaxel is referred to as carboplatin-based chemotherapy in the present assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results for research question 1: patients with programmed death ligand-1 (PD-L1) expression < 50%

Study pool and study characteristics

The KEYNOTE 407 study was used for the benefit assessment of pembrolizumab + carboplatin-based chemotherapy in comparison with the ACT.

KEYNOTE 407 is an ongoing, randomized, double-blind, controlled parallel-group study comparing pembrolizumab + carboplatin-based chemotherapy with carboplatin-based chemotherapy.

The study included adults with histologically or cytologically confirmed diagnosis of squamous NSCLC in the metastatic stage (stage IV according to the American Joint Committee on Cancer (AJCC) classification). Patients had to have received no prior systemic treatment for this stage.

A total of 559 patients were randomly allocated to the intervention arm (pembrolizumab + carboplatin-based chemotherapy: N = 278) or to the comparator arm (carboplatin-based chemotherapy: N = 281) in a 1:1 ratio. Patients in the intervention arm received a maximum of 35 cycles of 200 mg pembrolizumab as 30-minute infusion every 3 weeks as well as 4 cycles of carboplatin-based chemotherapy consisting of either paclitaxel or nab-paclitaxel every 3 weeks. Patients in the comparator arm received placebo for pembrolizumab and carboplatin-based chemotherapy following the same regimen as the one implemented in the intervention arm.

Primary outcome of the study was overall survival and progression-free survival. Patient-relevant secondary outcomes "symptoms", "health status", "health-related quality of life" and "adverse events (AEs)".

Implementation of the Pharmaceutical Directive on the use of carboplatin

In the first-line treatment, carboplatin is only approved in combination with nab-paclitaxel for the treatment of NSCLC, but not in combination with other third-generation cytostatic agents. According to Appendix VI to Section K of the pharmaceutical directive, the prescribability for carboplatin in the off-label use is restricted to patients for whom platinum-based combination therapy with a third-generation cytostatic agent such as paclitaxel, docetaxel or gemcitabine is an option. In each case, the choice of the platinum component (carboplatin or cisplatin) should

be based on the different toxicity profile of the two substances and on the existing comorbidities.

In the KEYNOTE 407 study, treatment with a carboplatin-based chemotherapy was not explicitly restricted according to these criteria. The company addressed the question of whether treatment with carboplatin was in compliance with the criteria of the pharmaceutical directive within a retrospective interview. For this purpose, the investigator was to justify the decision for treatment with a carboplatin-based combination chemotherapy on an individual basis. It was thus possible to form a subpopulation of the study including patients treated in accordance with the criteria of the pharmaceutical directive. It was assumed that these patients essentially met the criteria of the pharmaceutical directive for the off-label use of carboplatin in the present therapeutic indication.

Subpopulation relevant for the research question

The subpopulation of patients with PD-L1 expression < 50% included in the KEYNOTE 407 study who had moreover received treatment in accordance with the criteria of the pharmaceutical directive for off-label use of carboplatin is relevant for the present research question. In its dossier, the company presented analyses of a subpopulation (N = 157 in the intervention arm and N = 153 in the comparator arm) who met these criteria. This subpopulation represents the patient population relevant for the present research question and is used for the benefit assessment.

Switch of treatment from the comparator arm to monotherapy with pembrolizumab after disease progression

After confirmed disease progression and suitability, patients in the KEYNOTE 407 study could switch from the comparator arm to monotherapy with pembrolizumab in line with the protocol. For patients with PD-L1 expression ≥ 1%, this switch of treatment corresponds to the approved use of pembrolizumab in second-line treatment.

At the time point of the data cut-off of 3 April 2018, as many as 35 (22.9%) patients had switched from the comparator arm to treatment with pembrolizumab.

Methods used for the analysis of the outcome on overall survival in the relevant subpopulation unclear

When describing the operationalization of the outcome “overall survival”, the company stated that patients who had switched from the control arm to monotherapy with pembrolizumab were censored in the statistical analyses at the time point of the treatment switch. However, in connection with the ITT analyses, the result tables indicate that the observation was censored at the time ´point of the data cut-off.

The results on overall survival presented by the company were thus not usable due to these contradictory data. Meaningful interpretation requires an intention to treat (ITT) analysis with censoring at the time point of the last observation or the data cut-off.

Risk of bias

The risk of bias across outcomes was rated as low for the KEYNOTE 407 study. The risk of bias for the outcomes on "symptoms" (recorded using the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 [EORTC QLQ-LC13]), "health-related quality of life" (recorded using the EORTC QLQ-C30 functional scales) and "discontinuation due to AEs" is also rated as low. The certainty of conclusions for the outcome "discontinuation due to AEs" is restricted despite a low risk of bias. The risk of bias for the outcomes "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)", "immune-related AEs" and "immune-related severe AEs (CTCAE grade ≥ 3)" was rated as high.

Mortality

Overall survival

There are no usable analyses for this outcome. Hence, there was no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; an added benefit is therefore not proven.

Morbidity

Symptoms, recorded using the EORTC QLQ-C30 (symptom scales)

None of the EORTC QLQ-C30 symptoms scales (dyspnoea, fatigue, insomnia, pain, appetite loss, diarrhoea, nausea and vomiting, constipation) showed a statistically significant difference between the treatment arms. Hence, there was no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy for these outcomes; an added benefit is therefore not proven.

Symptoms, recorded using the EORTC QLQ-LC13 (symptom scales)

- Dysphagia

A statistically significant difference in favour of pembrolizumab + carboplatin-based chemotherapy was shown between the treatment groups for the outcome "dysphagia". This resulted in an indication of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

- Dyspnoea, pain (thorax), pain (arm/shoulder), pain (other), cough, haemoptysis, alopecia, sore mouth, peripheral neuropathy

No statistically significant difference between the treatment groups was shown for each of the following outcomes: dyspnoea, pain (thorax), pain (arm/shoulder), pain (other), cough, haemoptysis, alopecia, sore mouth, peripheral neuropathy. Hence, there was overall no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy for these outcomes; an added benefit is therefore not proven.

Health status (European Quality of Life-5 Dimension [EQ-5D] visual scale [VAS])

The dossier contained no usable data for the outcome "health status" measured with the EQ-5D VAS. Hence, there was no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30 (functional scales)

- Physical functioning

A statistically significant difference between the treatment groups in favour of pembrolizumab + carboplatin-based chemotherapy was shown for the outcome "physical functioning". This resulted in an indication of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

- Global health status, emotional functioning, cognitive functioning, role functioning, social functioning

There was no statistically significant difference between the treatment groups for the outcomes "global health status", "emotional functioning", "cognitive functioning", "role functioning", "social functioning". Hence, there was overall no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), immune-related SAEs

No usable data were available for the outcomes "SAEs" and "immune-related SAEs". This resulted in no hint of greater or lesser harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

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

Discontinuation due to AEs, immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for the outcomes "discontinuation due to AEs", and "immune-related severe AEs (CTCAE grade ≥ 3)". This resulted in no hint of greater or lesser harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; greater or lesser harm is therefore not proven.

Immune-related AEs

A statistically significant difference between the treatment arms to the disadvantage of pembrolizumab + carboplatin-based chemotherapy was shown for the outcome "immune-related AEs". This resulted in a hint of greater harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy

Results for research question 2: patients with PD-L1 expression > 50%

Study pool

No randomized controlled trials (RCTs) of direct comparison were identified for the assessment of the added benefit of pembrolizumab + carboplatin-based chemotherapy in patients with PD-L1 expressions ≥ 50% in comparison with the ACT. Therefore, the company presented an adjusted indirect comparison with the common comparator carboplatin-based chemotherapy for the assessment of the added benefit of pembrolizumab + carboplatin-based chemotherapy in patients with PD-L1 expressions ≥ 50%.

The KEYNOTE 407 study on the comparison of pembrolizumab + carboplatin-based chemotherapy with carboplatin-based chemotherapy was identified for the intervention. The studies KEYNOTE 042 and KEYNOTE 024 on the comparison of pembrolizumab (monotherapy) with carboplatin-based chemotherapy were identified for the comparator. For the KEYNOTE 024 study, only a subpopulation of 6 patients is relevant for the benefit assessment in the present research question. Due to the low number of patients from the KEYNOTE 024 study, the company excluded these patients from the indirect comparison. Therefore, the studies KEYNOTE 407 and KEYNOTE 042 are used for the indirect comparison.

Study characteristics

Study with the intervention: KEYNOTE 407

The KEYNOTE 407 study is also used for the assessment of the added benefit of research question 1 (patients with PD-L1 expression < 50%). The description of the study design can be found in research question 1 of the executive summary.

Study with the ACT: KEYNOTE 042

KEYNOTE 042 is an ongoing, randomized, open-label, controlled parallel-group study. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. A total of 1274 patients were randomly allocated to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637) in a 1:1 ratio. The study included adults with histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC, whose tumours expressed PD-L1 ≥ 1%. Prior systemic treatment was not allowed in the studies. The treatment option (carboplatin + paclitaxel or carboplatin + pemetrexed) suitable for the patient in case of randomization to the comparator arm was specified by an investigator on an individual basis.

Patients in the intervention arm received 200 mg pembrolizumab as 30-minute infusion every 3 weeks for a maximum of 35 cycles. Patients in the control arm received 6 cycles of a carboplatin-based chemotherapy every 3 weeks, consisting of either paclitaxel or pemetrexed.

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

Implementation of the Pharmaceutical Directive on the use of carboplatin

As with research question 1 (patients with PD-L1 expression < 50%), the criteria of Appendix IV to Section K of the Pharmaceutical Directive must be considered in carboplatin treatment. Neither for the KEYNOTE 407 study nor for the KEYNOTE 042 study, treatment with carboplatin-based chemotherapy was explicitly limited according to the criteria of the Pharmaceutical Directive. Therefore, the company conducted retrospective interviews with the investigators, as it had done for research question 1. For this purpose, the investigator was to justify the decision for treatment with a carboplatin-based combination chemotherapy on an individual basis. It was thus possible to form a subpopulation of the study including patients treated in accordance with the criteria of the pharmaceutical directive. It was assumed that these patients essentially met the criteria of the pharmaceutical directive for the off-label use of carboplatin in the present therapeutic indication.

Subpopulation of the studies relevant for the research question

The present research question includes patients with metastatic squamous NSCLC and PD-L1 expression ≥ 50%, who had moreover received treatment with carboplatin in accordance with the criteria of the pharmaceutical directive for off-label use (Appendix VI to Section K). Moreover, a carboplatin-based chemotherapy in combination with either paclitaxel or nab-paclitaxel is the only suitable common comparator for an adjusted indirect comparison with the studies KEYNOTE 407 and KEYNOTE 042. For the studies KEYNOTE 407 and KEYNOTE 042, the company presented analyses of the subpopulations who met the criteria described above. In the KEYNOTE 407 study, these were N = 55 patients in the intervention arm and N = 53 patients in the comparator arm. In the KEYNOTE 042 study, N = 57 patients were included in the intervention arm and N = 63 patients were included in the comparator arm. The analyses presented by the company represent the subpopulation relevant for the present research question.

Similarity of the studies in the adjusted indirect comparison

Differences between the studies KEYNOTE 407 and KEYNOTE 042 are shown in the common comparator: In the KEYNOTE 407 study, patients in the comparator arm received carboplatin-based chemotherapy with either paclitaxel or nab-paclitaxel; in the KEYNOTE 042 study, all patients of the relevant subpopulation in the comparator arm exclusively received paclitaxel in combination with carboplatin. Moreover, carboplatin-based chemotherapy was administered for a total of 4 cycles in the KEYNOTE 407 study, whereas patients in the KEYNOTE 042 study received 6 cycles.

The assumption of similarity for the indirect comparison did not have to be discarded due to the described differences between the studies. However, potential impacts of these differences have to be investigated for the individual outcomes.

Switch of treatment from the comparator arm to monotherapy with pembrolizumab after disease progression

In both studies, patients of the comparator arm had switched to monotherapy with pembrolizumab after confirmed disease progression. This treatment is approved in the corresponding line of treatment.

In the KEYNOTE 407 study, these were 24.5% (n = 13) patients in the control arm of the relevant subpopulation; in the KEYNOTE 042 study, the proportion amounted to 11.1% (n = 7).

Methods used for the analysis of the outcome on overall survival in the relevant subpopulation unclear

When describing the operationalization of the outcome "overall survival", the company stated that patients who had switched from the control arm to monotherapy with pembrolizumab were censored in the statistical analyses at the time point of the treatment switch. However, in connection with the ITT analyses, the result tables indicate that the observation was censored at the time point of the data cut-off.

The results on overall survival presented by the company were thus not usable due to these contradictory data. Meaningful interpretation requires an ITT analysis with censoring at the time point of the last observation or the data cut-off.

Results

Overall consideration of the available data results in the following picture:

There are no usable data for the outcomes of the categories "mortality", "morbidity" and "health-related quality of life"; some of the outcomes were not recorded in the studies. For the outcomes of the category "side effects", usable analyses were only available for the outcomes "discontinuation due to AEs" and "severe AEs (CTCAE grade ≥ 3)". Therefore, the present data situation does not permit a benefit assessment with subsequent weighing of positive and negative effects despite the general suitability of the studies KEYNOTE 407 and KEYNOTE 042 for the indirect comparison. Overall, the data on the indirect comparison presented by the company are unsuitable to derive an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel versus pembrolizumab in first-line treatment of metastatic squamous NSCLC with a PD-L1 expression ≥ 50% in adults. This resulted in no hint of an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with pembrolizumab; an added benefit is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with the ACT are assessed as follows:

Research question 1: patients with PD-L1 expression < 50%

In the overall consideration of the results, there are positive effects and 1 negative effect. Since usable analyses on overall survival are not available for the relevant subpopulation, a balancing of positive and negative effects for the overall conclusion on the added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with the ACT is not possible.

Overall, an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with carboplatin in combination with either paclitaxel or nab-paclitaxel was thus not proven for first-line treatment of patients with metastatic squamous NSCLC with a PD-L1 < 50%.

Research question 2: patients with PD-L1 expression ≥ 50%

An added benefit is not proven, since the company presented no suitable data for the assessment of the added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with pembrolizumab in first-line treatment of adults with metastatic squamous NSCLC with a PD-L1 expression ≥ 50%.

Table 3 presents a summary of the probability and extent of the added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel.

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

Table 3: Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel – Probability and extent of added benefit

Research question	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
1	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression < 50%	Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel) *or* **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or **paclitaxel**; see also Appendix VI to Section K of the pharmaceutical directive) *or* **carboplatin in combination with nab-paclitaxel**	Added benefit not proven
2	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression ≥ 50%	Pembrolizumab as monotherapy	Added benefit not proven

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: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to the IASLC and the UICC), without medical indication for definitive local therapy.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; UICC: Union for International Cancer Control

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 pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with the ACT for the first-line treatment of adults with metastatic squamous NSCLC.

The research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel

Research question	**Subindication**	**ACT**[a]
1	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression < 50%	Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel) *or* **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or **paclitaxel**; see also Appendix VI to Section K of the pharmaceutical directive [3]) *or* **carboplatin in combination with nab-paclitaxel**
2	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression ≥ 50%.	Pembrolizumab as monotherapy

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: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to the IASLC and the Union for International Cancer Control UICC), without medical indication for definitive local therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; UICC: Union for International Cancer Control

The company followed the G-BA's specification on the ACT for both research questions. For research question 1, the company chose carboplatin in combination with either paclitaxel or nab-paclitaxel from the options presented.

Unless otherwise stated, carboplatin-based chemotherapy in combination with either paclitaxel or nab-paclitaxel is referred to as carboplatin-based chemotherapy in the present assessment.

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 Research question 1: patients with PD-L1 expression < 50%

2.3.1 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 + carboplatin-based chemotherapy (status: 24 January 2019)
- bibliographical literature search on pembrolizumab + carboplatin-based chemotherapy (last search on 8 January 2019)
- search in trial registries for studies on pembrolizumab + carboplatin-based chemotherapy (last search on 9 January 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab + carboplatin-based chemotherapy (last search on 10 April 2019)

The check identified no additional relevant study.

2.3.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based 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 407	Yes	Yes	No
a: In combination with either paclitaxel or nab-paclitaxel. b: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

The study pool includes the KEYNOTE 407 study. The study pool concurred with that of the company.

Section 2.3.1 contains a reference list for the studies included.

2.3.1.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
KEYNOTE 407	RCT, double-blind, parallel	Adult patients with histologically or cytologically confirmed stage IV squamous[c] NSCLC, ECOG ≤ 1 and without prior systemic treatment[d]	▪ Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (N = 278) ▪ Carboplatin and either paclitaxel or nab-paclitaxel (N = 281) Relevant subpopulation thereof[e]: ▪ Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (n = 157) ▪ Carboplatin and either paclitaxel or nab-paclitaxel (n = 153)	▪ Screening: 28 days prior to the start of treatment ▪ Treatment: Until complete response or until progression, unacceptable toxicity, occurrence of intercurrent diseases that make further treatment impossible, pregnancy, discontinuation of treatment due to decision by the physician or the patient or after a maximum of 35 cycles of pembrolizumab[f] ▪ Follow-up[g]: at most until death	125 centres in Australia, Canada, China, Germany, France, Italy, Japan, Mexico, Poland, Russia, South Korea, Spain, Thailand, The Netherlands, Turkey, Hungary and the United States 08/2016–ongoing Data cut-off: 3 April 2018	Primary: overall survival PFS Secondary: morbidity, health-related quality of life, AEs

a: In combination with either paclitaxel or nab-paclitaxel.
b: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c: Patients with mixed histology could be included in the study if the sample comprised squamous components.
d: For patients who had received adjuvant or neoadjuvant therapy, treatment had to be terminated at least 12 months prior to the development of the metastatic disease.
e: The relevant subpopulation comprised patients with PD-L1 expressing tumours (TPS < 50%) who had been treated in accordance with the criteria of the pharmaceutical directive for off-label use (Appendix VI to Section K [3]) of carboplatin (TPC subpopulation).
f: Patients in the intervention arm could temporarily discontinue treatment after complete and confirmed response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab as monotherapy at the investigator's discretion ("second course phase") after subsequent confirmed progression (if certain conditions regarding treatment duration and disease status were met).
g: Outcome-specific information is provided in Table 8.

AE: adverse event; ECOG: Eastern Cooperative Oncology Group; n: relevant subpopulation; N: number of randomized (included) patients; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; TPC: treatment of physician's choice; TPS: Tumour Proportion Score; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Study	Intervention	Comparison
KEYNOTE 407	Pembrolizumab 200 mg IV (infusion administered over 30 minutes) every 3 weeks for a maximum of 35 cycles + 4 cycles of carboplatin-based combination chemotherapy: ▪ Carboplatin area under the curve (AUC) 6 mg/mL/min (max. 900 mg) IV as infusion administered over 15 to 60 minutes on day 1 of the 3-week cycle and ▪ on day 1 of the 3-week cycle 200 mg/m² IV paclitaxel as infusion administered over 3 hours or on days 1, 8 and 15 of the 3-week cycle 100 mg/m² IV nab-paclitaxel as infusion administered over 30 minutes	Placebo solution IV, infusion administered over 30 minutes, every 3 weeks for a maximum of 35 cycles + 4 cycles of carboplatin-based combination chemotherapy: ▪ Carboplatin AUC 6 mg/mL/min (max. 900 mg) IV as infusion administered over 15 to 60 minutes on day 1 of the 3-week cycle, and ▪ on day 1 of the 3-week cycle 200 mg/m² IV paclitaxel as infusion administered over 3 hours or on days 1, 8 and 15 of the 3-week cycle 100 mg/m² IV nab-paclitaxel as infusion administered over 30 minutes
	Dose adjustments in case of toxicities ▪ Allowed for carboplatin and paclitaxel/nab-paclitaxel in line with the protocol ▪ Not allowed for pembrolizumab (treatment could be discontinued) **Pretreatment** ▪ Adjuvant or neoadjuvant therapy, the last treatment had to be administered at least 12 months prior to the development of the metastatic disease **Non-permitted pretreatment** ▪ Systemic treatment of stage IIIB and IV NSCLC **Non-permitted concomitant treatment** ▪ Other antineoplastic systemic chemotherapy or biologic treatments ▪ Other chemotherapies or immunotherapies ▪ Systemic corticosteroids (treatment > 7 days), expect for the treatment of AEs or as premedication of a chemotherapy used in the study ▪ Radiotherapy ▪ Live vaccines	

a: In combination with either paclitaxel or nab-paclitaxel.
b: Following the guidelines of the American Society of Clinical Oncology (ASCO).
AE: adverse event; AUC: area under the curve; IV: intravenous; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

Study design

KEYNOTE 407 is an ongoing, randomized, double-blind, controlled parallel-group study. The study compares pembrolizumab + carboplatin-based chemotherapy with a carboplatin-based chemotherapy. A total of 559 patients were randomly allocated to the intervention arm (pembrolizumab + carboplatin-based chemotherapy: N = 278) or to the comparator arm (carboplatin-based chemotherapy: N = 281) in a 1:1 ratio. Randomization was stratified by type of taxane-based chemotherapy (paclitaxel/nab-paclitaxel), PD-L1 expression (< 1%/≥ 1%) and

geographical region (East Asia/not East Asia). The study included adults with histologically or cytologically confirmed diagnosis of squamous NSCLC in the metastatic stage (stage IV according to the AJCC classification). Patients had to have received no prior systemic treatment for this stage. For patients who had received adjuvant or neoadjuvant therapy, treatment had to be terminated at least 12 months prior to the development of metastases. The ECOG-PS had to be 0 or 1 in the included patients. Patients with active brain metastases were excluded from the study.

In the study, the PD-L1 expression of the tumour tissue was determined by means of the Dako Commercial Ready Assay (monoclonal, PD-L1-targeted, antibody of the 22C3 clone) using immunohistochemistry. In doing so, the Tumour Proportion Score (TPS) was determined, which indicates the percentage of the live tumour cells whose membranes are partially or completely stained. Unless stated otherwise, the specified PD-L1 expression refers to the analyses with TPS in the present dossier assessment.

Patients in the intervention arm received 200 mg pembrolizumab as 30-minute infusion every 3 weeks (maximum treatment duration: 35 cycles) as well as 4 cycles of carboplatin-based chemotherapy consisting of either paclitaxel or nab-paclitaxel every 3 weeks. Patients in the comparator arm received placebo for pembrolizumab and carboplatin-based chemotherapy following the same regimen as the one implemented in the intervention arm. Administration of pembrolizumab, carboplatin and nab-paclitaxel was in compliance with the specifications of the SPC [4-7] or the pharmaceutical directive for off-label use (Appendix VI to Section K [3]) (see below). Neither the SPC [8] nor the pharmaceutical directive on off-label use (Appendix VI to Section K [3]) contains information on the dosage of paclitaxel in combination with carboplatin. In the study, paclitaxel was administered as 3-hour infusion at a dosage of 200 mg/m² body surface area.

Primary outcome of the study was “overall survival” and “progression-free survival (PFS)”. Patient-relevant secondary outcomes were “symptoms”, “health status”, “health-related quality of life” and “AEs”.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation due to decision by the physician or the patient. Treatment in the intervention arm was generally restricted by the maximum number of allowed cycles of pembrolizumab (35 cycles); none of the patients in the study achieved this maximum number.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. There were no restrictions regarding the type of subsequent therapy. Moreover, suitable patients with disease progression were allowed to switch from treatment with the comparator therapy to monotherapy with pembrolizumab. At the time point of the primary data cut-off of 3 April 2018, the proportion of patients with subsequent therapy that was administered outside of the study protocol was 15.8% (n=44) in the intervention arm and approx. 42% (n=118) in the comparator arm (see Table 34

of the full dossier assessment). In the comparator arm, 75 (26.7%) patients had switched to treatment with pembrolizumab as monotherapy in accordance with the protocol.

Implementation of the Pharmaceutical Directive on the use of carboplatin

In first-line treatment, carboplatin is only approved in combination with nab-paclitaxel for the treatment of NSCLC [4], but not in combination with other third-generation cytostatic agents. According to the current version of Appendix VI to Section K of the Pharmaceutical Directive [3], carboplatin in the off-label use can be prescribed for patients with advanced NSCLC. Thereby, application in accordance with the Pharmaceutical Directive is suitable for patients for whom platinum-based combination therapy with a third-generation cytostatic agent such as paclitaxel, docetaxel or gemcitabine is an option. In each case, the choice of the platinum component (carboplatin or cisplatin) should be based on the different toxicity profiles of the two substances and on the existing comorbidities (e.g. existing neuropathy or relevant hearing impairment, particular susceptibility to nausea, renal insufficiency or cardiac failure) [3]. Patients who are eligible for approved treatments should not be treated with a carboplatin-based chemotherapy.

In the KEYNOTE 407 study, treatment with a carboplatin-based chemotherapy was not explicitly restricted according to these criteria. The company addressed the question of whether treatment with carboplatin was in compliance with the criteria of the pharmaceutical directive within a retrospective interview (referred to by the company as “treatment of physician’s choice [TPC] interview”). For this purpose, the investigator was to justify the decision for treatment with a carboplatin-based combination chemotherapy on an individual basis. It was thus possible to form a subpopulation of the study including patients treated in accordance with the criteria of the pharmaceutical directive. This subpopulation is hereinafter referred to as “TPC population” (referred to as “TPC survey population” by the company).

The TPC population comprised patients:

- whom the investigator deemed unsuitable for cisplatin-based treatment and who therefore received carboplatin-based treatment.
- whom the investigator deemed suitable for cisplatin-based treatment, but who were to receive carboplatin-based treatment due to the expected better benefit-risk balance or better risk profile.

In its dossier, the company provided partially unclear information on the reasons for the allocation of the patients to carboplatin-based chemotherapy. Therefore, a slight uncertainty remains whether all points of the specifications stipulated in the Pharmaceutical Directive for off-label use were completely implemented (see Section 2.6.4.1 of the full dossier assessment). However, it was assumed that the patients of the TPC population essentially met the criteria of the pharmaceutical directive for the off-label use (Appendix VI to Section K [3]) of carboplatin in the present therapeutic indication.

Subpopulation relevant for the research question

The KEYNOTE 407 study included patient irrespective of the PD-L1 expression of the tumour cells. Only the subpopulation of the included patients with PD-L1 expression < 50% who had moreover received treatment in accordance with the criteria of the pharmaceutical directive for off-label use (Appendix VI to Section K [3]) of carboplatin is relevant for the present research question. In its dossier, the company presented analyses of a subpopulation (N = 157 in the intervention arm and N = 153 in the comparator arm) who met these criteria. This subpopulation represents the patient population relevant for the present research question and is used for the benefit assessment.

Data cut-offs

The KEYNOTE 407 study is still ongoing. Two data cut-offs are available so far:

- First data cut-off (27 October 2017): scheduled first interim analysis on the outcome "objective response rate", after approx. 200 patients had undergone a follow-up observation period of 28 weeks.
- Second data cut-off (3 April 2018): prespecified second interim analysis after approx. 332 events had occurred in the outcome "PFS".

According to the study protocol, a third interim analysis is scheduled after achievement of approx. 415 events in the outcome "PFS". The final data cut-off for "overall survival" was scheduled after approx. 361 death had been reached.

In Module 4 C, the company presents analyses on the data cut-off of 3 April 2018. This was used for the present benefit assessment.

Follow-up

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE 407	
Mortality	
Overall survival	▪ After end of treatment: every 3 months until death
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)	▪ Until 30 days after the last dose of the study medication
Health status (EQ-5D VAS)	▪ Until 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	▪ Until 30 days after end of the last dose of the study medication
Side effects	
AEs	▪ Until 30 days after the last dose of the study medication (or until initiation of a new antineoplastic treatment; whichever occurred first)
SAEs	▪ Until 90 days after the last dose of the study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment is initiated, whichever occurred first)

a: In combination with either paclitaxel or nab-paclitaxel.

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-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Hence, the observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened in the KEYNOTE 407 study because they were only recorded for the time period of treatment with the study medication (plus 30 or 90 days). 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”.

Characteristics of the study population

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

Table 9: Characteristics of the study populations – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Study Characteristics Category	Pembrolizumab + carboplatin-based chemotherapy[a]	Carboplatin-based chemotherapy[a]
KEYNOTE 407	N[b] = 157	N[b] = 153
Age [years], mean (SD)	66 (9)	65 (8)
Sex [F/M], %	20/80	17/83
Ethnicity, n (%)		
White	114 (72.6)	110 (71.9)
Non-white[c]	41 (26.1)[d]	36 (23.5)[d]
Unknown	2 (1.3)	7 (4.6)
Region, n (%)		
EU	73 (46.5)	63 (41.2)
Non-EU	84 (53.5)	90 (58.8)
Smoking status, n (%)		
Never-smoker	11 (7.0)	10 (6.5)
Former	99 (63.1)	106 (69.3)
Active	47 (29.9)	37 (24.2)
ECOG PS, n (%)		
0	43 (27.4)	50 (32.7)
1	114 (72.6)	103 (67.3)
Disease stage, n (%)		
IV	157 (100.0)	153 (100.0)
Metastases, n (%)	ND[e]	ND[e]
Time since initial diagnosis [months]		
Mean (SD)	5.1 (19.9)	4.7 (9.1)
Median [min; max]	1.4 [0.0; 212.6]	1.4 [0.0; 48.8]
Tumour size at start of the study [mm]		
Mean (SD)	108.8 (67.0)[f]	106.9 (67.3)[f]
Median [min; max]	94.1 [15.2; 341.5]	95.9 [11.1; 376.5]
Brain metastases, n (%)		
Yes	8 (5.1)	12 (7.8)
No	149 (94.9)	141 (92.2)
Prior therapies, n (%)		
Adjuvant/neoadjuvant prior therapy	3 (1.9)	6 (3.9)
Taxane-based chemotherapy, n (%)		
Carboplatin + paclitaxel	84 (53.5)	72 (47.1)
Carboplatin + nab-paclitaxel	73 (46.5)	81 (52.9)
Treatment discontinuation, n (%)	ND[g]	ND[g]
Study discontinuation, n (%)	ND[g]	ND[g]

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a] (continued)

a: In combination with either paclitaxel or nab-paclitaxel.
b: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant
c: "Non-white" includes Native Americans or Native Alaskans, Asians, Black or African Americans and Native Hawaiians or Native Pacific Islanders.
d: Institute's calculation
e: Data on stage M1, M1A, M1B and MX tumour metastases are not available for the relevant subpopulation.
f: Only the data of 154 patients (in the intervention arm) or 152 patients (in the comparator arm) were considered in the calculation.
g: There was no information on treatment and study discontinuations for the relevant subpopulation.
F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PD-L1: programmed cell death ligand 1; PS: performance status; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and clinical characteristics of the relevant subpopulation were sufficiently balanced between the study arms.

The mean age of the patients included in the relevant subpopulation was approx. 65 years, the majority were male, most of them were white. Half of the patients were from the EU. At the start of the study, the majority of the patients had an ECOG-PS of 1 and no brain metastases. Median initial diagnosis was 1.4 months ago.

Switch of treatment from the comparator arm to monotherapy with pembrolizumab after disease progression

In line with the protocol and after confirmed disease progression and suitability, patients in the KEYNOTE 407 study could switch from the comparator arm to monotherapy with pembrolizumab 21 days after the last treatment with the study medication. This treatment is an approved therapy in the present line of treatment for patients with PD-L1 expressions ≥ 1% [6,7]. In the control arm, not every patient of the relevant subpopulation of the KEYNOTE 407 study had a PD-L1 expression ≥ 1%. Half of the patients in the control arm (n = 76 [49.7%]) had a PD-L1 expression < 1%.

At the time point of the data cut-off of 3 April 2018, as many as 35 (22.9%) patients had switched from the comparator arm to monotherapy with pembrolizumab. In the relevant subpopulation of the study, also patients with a PD-L1 expression < 1% switched from the control arm to monotherapy with pembrolizumab and thus to an unapproved subsequent therapy. The company presented the Kaplan-Meier curve for the time to treatment switch (Figure 3 in Appendix A of the full dossier assessment). The figure shows that the majority of these treatment switches took place in the period between 3 and 9 months. Overall, large proportions of patients had thus switched from the control arm to monotherapy with pembrolizumab at early time points.

Methods used for the analyses of the outcome "overall survival" in the relevant subpopulation unclear

The analyses of the outcome "overall survival" presented by the company were not interpretable due to contradictory information provided by the company. This is explained below:

When describing the operationalization of the outcome "overall survival" in Module 4 C of its dossier, the company stated that patients who had switched from the control arm to monotherapy with pembrolizumab were censored in the statistical analyses at the time point of the treatment switch. In the study documents of the KEYNOTE 407 study, "overall survival" was operationalized as period between randomization and death for any reason. The analysis on "overall survival" planned primarily in the study is an ITT analysis. Accordingly, the result tables in Module 4 C on the ITT analyses indicate that the observation was censored at the time point of the data cut-off. This is contrary to the data of the operationalization. Comparison of the Kaplan-Meier curves for the treatment switch and "overall survival" cannot resolve the discrepancy (see Figure 2 and Figure 3 in Appendix A of the full dossier assessment).

Altogether, the data on the analyses of the outcome "overall survival" are contradictory. The results presented by the company are therefore not usable. Meaningful interpretation requires an ITT analysis with censoring at the time point of the last observation or the data cut-off. Due to the partially unapproved treatment switch, it must also be checked whether the corresponding event time analyses show an effect modification by the characteristic "PD-L1 expression (≥ 1%, < 1%)".

Observation duration

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

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

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + carboplatin-based chemotherapy[a]**	**Carboplatin-based chemotherapy[a]**
KEYNOTE 407	N = 157	N = 152
Treatment duration [months]		
Median [min; max]	5.5 [0.0; 17.9]	4.4 [0.0; 16.6]
Mean (SD)	6.4 (4.3)	5.2 (3.5)
Observation period [months]		
Overall survival		
Median [min; max]	8.2 [0.4; 18.2]	7.2 [0.4; 18.5]
Mean (SD)	8.5 (4.2)	7.8 (4.0)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (SAEs)	No usable data	

a: In combination with either paclitaxel or nab-paclitaxel.
ASaT: All Subjects as Treated; max: maximum; min: minimum; N: number of analysed patients (ASaT); ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

In the KEYNOTE 407 study, the median treatment duration and the median observation period on "overall survival" are largely comparable between the study arms.

In module 4 C of its dossier, the company provided data on the observation period of SAEs in the KEYNOTE 407 study. However, these data are not interpretable for the present benefit assessment, because patients who switched from the control arm to monotherapy with pembrolizumab were only considered until the time point of the treatment switch. As already described above, a relevant number of patients in the KEYNOTE 407 study switched from the control arm to monotherapy with pembrolizumab. Monotherapy with pembrolizumab was to be initiated 21 days after treatment discontinuation in the comparator arm. Follow-up observation of the patients who switched treatment in the comparator arm ended with the start of the new therapy. However, follow-up observation for the outcome "SAEs" was planned to take 90 days. Thus, more than 2 months of information are lacking for patients who switched treatment (see also Section 2.6.4.2 of the full dossier assessment).

For the intervention and comparator arms, information on the observation periods is lacking for the outcomes "morbidity", "health-related quality of life" as well as for further outcomes of the category "side effects". It was assumed, however, that for these outcomes the difference in the observation period between the study arms was similar to the difference in treatment duration, because the follow-up observation was limited (see Table 8 for the planned follow-up observation).

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based 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 407	Yes	Yes	Yes	Yes	Yes	Yes	Low

a: In combination with either paclitaxel or nab-paclitaxel.
RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the KEYNOTE 407 study. This concurs with the company's assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.4.3.2 of the full dossier assessment):

- Mortality
  - All-cause mortality
- Morbidity
  - Symptoms recorded with the symptom scales of the instruments EORTC QLQ-C30 and Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13)
  - Health status measured with the EQ-5D VAS
- health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-related AEs, SAEs and severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 C) (see Section 2.6.4.3.2 of the full dossier assessment).

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

Table 12: Matrix of the outcomes – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Study	Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-LC13)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Further specific AEs
KEYNOTE 407	No[b]	Yes	No[b]	Yes	No[b]	Yes	Yes	Yes	No[b]	Yes	No[b]

a: In combination with either paclitaxel or nab-paclitaxel.
b: No usable data available; for reasons, see Sections 2.3.1.2 as well as 2.6.4.2 and 2.6.4.3.2 of the full dossier assessment.

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-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; TPS: Tumour Proportion Score; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Study		Outcomes										
	Study level	Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-LC13)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Further specific AEs
KEYNOTE 407	L	–[b]	L	–[b]	L	–[b]	L[c]	H[d]	H[d]	–[b]	H[d]	–[b]

a: In combination with either paclitaxel or nab-paclitaxel.
b: No usable data available; for reasons, see Sections 2.3.1.2 as well as 2.6.4.2 and 2.6.4.3.2 of the full dossier assessment.
c: Despite low risk of bias, a restricted certainty of results was assumed for the outcome "discontinuation due to AEs" (see Section 2.6.4.2 of the full dossier assessment).
d: Missing data on the observation period for the intervention and control arms.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organization 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-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

There are no usable analyses for "overall survival", "health status (measured with the EQ-5D VAS)", "SAEs", ""immune-related SAEs" and further specific AEs (see Sections 2.3.1.2 as well as 2.6.4.2 and 2.6.4.3.2 of the full dossier assessment); therefore, no assessment of the risk of bias was conducted for these outcomes.

The risk of bias was rated as low for the results on the outcomes "symptoms" (recorded with the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales) and "health-related quality of life" (recorded with the EORTC QLQ-C30 functional scales). Response to the questionnaires decreased and differed between the treatment arms during the course of the study. However, the majority of the missing observations can be explained by deaths. This concurs with the company's assessment.

The certainty of conclusions for the results of the outcome "discontinuation due to AEs" was restricted despite a low risk of bias (see Section 2.6.4.2 of the full dossier assessment).

There was a high risk of bias for the results of all other outcomes. Due to the lacking data on the observation period, the risk of bias for the results on the outcomes "severe AEs (CTCAE grade ≥ 3)", "immune-related AEs" and "immune-related severe AEs (CTCAE grade ≥ 3)" was rated as high. It could not be assessed whether there was a relevant number of incomplete observations due to potentially informative reasons (see Section 2.6.4.2 of the full dossier assessment).

However, the company rated the risk of bias for these outcomes as low.

2.3.2.3 Results

Table 14 summarizes the results on the comparison of pembrolizumab + carboplatin-based chemotherapy with carboplatin-based chemotherapy in the first-line treatment of patients with metastatic squamous NSCLC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

For the relevant subpopulation, the company only presented Kaplan-Meier curves on event time analyses for the outcome categories "morbidity" and "health-related quality of life" as well as "specific AEs" (except for the overall rates of the immune-related AEs and immune-related severe AEs) when the corresponding outcome showed a statistically significant effect between the treatment arms of the relevant subpopulation. The Kaplan-Meier curves on the presented event time analyses presented by the company are found in Appendix A of the full dossier assessment.

At the level of system organ classes (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), the company presented effect estimations from event time analyses for the relevant subpopulation on all AEs, severe AEs (CTCAE degree ≥ 3), on discontinuation due to AEs and immune-related AEs. At the level of the preferred term (PT) according to MedDRA, no event time analyses are available for the relevant subpopulation. For PTs, event rates without corresponding effect estimations are only presented if the corresponding SOC shows a statistically significant difference between the treatment arms in the event time analysis and certain threshold values for the frequencies are reached. Therefore, results on frequent side effects are only presented at SOC level in Appendix B of the full dossier assessment. Presentation of the frequent PTs is omitted due to incompleteness (see Section 2.6.4.3.2 of the full dossier assessment).

Table 14: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Study **Outcome category** **Outcome**	**Pembrolizumab + carboplatin-based chemotherapy[a]**		**Carboplatin-based chemotherapy[a]**		**Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]**
	L	**Median time to event in months [95% CI]** **Patients with event n (%)**	**L**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
KEYNOTE 407					
Mortality					
Overall survival	No usable analyses				
Morbidity					
EORTC QLQ-C30 (symptom scales)[b]					
Dyspnoea	156	8.5 [4.4; NC] 61 (39.1)	152	5.6 [3.5; NC] 66 (43.4)	0.79 [0.55; 1.13]; 0.191
Fatigue	156	1.9 [1.4; 2.4] 100 (64.1)	152	2.1 [1.5; 3.3] 93 (61.2)	1.02 [0.76; 1.36]; 0.912
Insomnia	156	10.4 [3.6; NC] 64 (41.0)	152	4.2 [2.9; NC] 69 (45.4)	0.83 [0.58; 1.17]; 0.283
Pain	156	4.4 [3.5; NC] 70 (44.9)	152	3.7 [2.6; 4.8] 80 (52.6)	0.72 [0.52; 1.00]; 0.053
Appetite loss	156	4.0 [3.0; 6.5] 78 (50.0)	152	6.2 [2.8; 6.9] 69 (45.4)	0.99 [0.71; 1.38]; 0.943
Diarrhoea	156	NA [5.8; NC] 54 (34.6)	152	11.3 [NC] 49 (32.2)	1.07 [0.72; 1.59]; 0.742
Nausea and vomiting	156	6.4 [3.4; NC] 70 (44.9)	152	4.2 [3.0; NC] 70 (46.1)	0.98 [0.69; 1.37]; 0.891
Constipation	156	9.0 [3.7; NC] 64 (41.0)	152	11.1 [4.2; 11.1] 54 (35.5)	1.01 [0.70; 1.47]; 0.958
EORTC QLQ-LC13 (symptom scales)[b]					
Dyspnoea	156	2.6 [2.0; 3.5] 92 (59.0)	152	2.6 [2.1; 3.7] 88 (57.9)	0.97 [0.72; 1.31]; 0.836
Pain (thorax)	156	NA 42 (26.9)	152	7.0 [6.3; NC] 55 (36.2)	0.69 [0.46; 1.04]; 0.074
Pain (arm/shoulder)	156	10.4 [6.7; NC] 55 (35.3)	152	11.1 [5.7; NC] 53 (34.9)	0.85 [0.58; 1.26]; 0.427
Pain (other)	156	3.6 [2.8; 6.7] 77 (49.4)	152	5.7 [3.7; 7.0] 66 (43.4)	1.10 [0.79; 1.54]; 0.569

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a] (continued)

Study Outcome category Outcome	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]
	L	Median time to event in months [95% CI] Patients with event n (%)	L	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
KEYNOTE 407					
Cough	156	NA [7.3; NC] 52 (33.3)	152	NA [6.3; NC] 47 (30.9)	0.95 [0.63; 1.41]; 0.784
Haemoptysis	156	NA 23 (14.7)	152	NA 26 (17.1)	0.78 [0.44; 1.39]; 0.402
Alopecia	156	0.8 [0.7; 0.9] 133 (85.3)	152	0.8 [0.7; 0.9] 125 (82.2)	1.09 [0.85; 1.40]; 0.500
Dysphagia	156	NA 25 (16.0)	152	NA 42 (27.6)	0.52 [0.31; 0.86]; 0.011
Sore mouth	156	NA [9.5; NC] 42 (26.9)	152	NA [8.5; NC] 43 (28.3)	0.83 [0.54; 1.29]; 0.417
Neuropathy peripheral	156	2.4 [2.1; 3.5] 89 (57.1)	152	2.6 [2.1; 3.0] 94 (61.8)	0.78 [0.58; 1.05]; 0.098
Health status (EQ-5D VAS)	No usable analyses				
Health-related quality of life					
EORTC QLQ-C30 (functional scales)[c,d]					
Global health status	156	3.6 [2.2; 6.4] 80 (51.3)	152	3.5 [2.1; 5.1] 79 (52.0)	0.89 [0.65; 1.23]; 0.488
Emotional functioning	156	NA 49 (31.4)	152	NA [6.1; NC] 53 (34.9)	0.77 [0.52; 1.15]; 0.205
Cognitive functioning	156	4.1 [3.2; NC] 71 (45.5)	152	3.5 [2.3; 6.2] 77 (50.7)	0.83 [0.60; 1.16]; 0.277
Physical functioning	156	3.5 [2.4; 9.5] 77 (49.4)	152	2.8 [2.1; 4.0] 91 (59.9)	0.71 [0.52; 0.96]; 0.028
Role functioning	156	3.1 [2.3; 3.7] 91 (58.3)	152	2.8 [1.8; 4.2] 85 (55.9)	0.98 [0.73; 1.32]; 0.896
Social functioning	156	4.0 [2.8; 7.8] 76 (48.7)	152	2.8 [2.1; 4.2] 81 (53.3)	0.87 [0.63; 1.20]; 0.388

(continued)

Table 14: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a] (continued)

Study Outcome category Outcome	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]
	L	Median time to event in months [95% CI] Patients with event n (%)	L	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value
KEYNOTE 407					
Side effects[e]					
AEs (additional information)	157	0.1 [0.1; 0.2] 153 (97.5)	152	0.1 [0.1; 0.2] 151 (99.3)	–
SAEs	No usable analyses				
Severe AEs (CTCAE grade ≥ 3)	157	1.9 [1.6; 2.7] 107 (68.2)	152	1.2 [0.7; 1.5] 118 (77.6)	0.69 [0.53; 0.90]; 0.006
Discontinuation due to AEs	157	NA [14.4; NC] 31 (19.7)	152	NA [12.9; NC] 19 (12.5)	1.38 [0.78; 2.44]; 0.274
Immune-related AEs	157	NA 41 (26.1)	152	NA 13 (8.6)	3.09 [1.66; 5.77]; < 0.001
Immune-related SAEs	No usable analyses				
Immune-related severe AEs (CTCAE grade ≥ 3)	157	NA 19 (12.1)	152	NA 8 (5.3)	2.28 [1.00; 5.20]; 0.051

a: In combination with either paclitaxel or nab-paclitaxel.
b: Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline.
c: Time to first deterioration; defined as decrease of the score by ≥ 10 points compared with baseline.
d: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 expression (TPS < 1% vs. ≥ 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and region (East Asia vs. not East Asia), 2-sided p-value (Wald test).
e: Cox proportional hazards model with treatment as covariate; 2-sided p-value (Wald test).
AE: adverse event; CI: 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; n: number of patients with at least one event; N: number of analysed patients; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; TPS: Tumour Proportion Score; 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 outcomes "symptoms" (measured with the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales) and "health-related quality of life" (measured with the EORTC QLQ-C30 functional scales), and at most hints, e.g. of an added benefit, can be derived for all other outcomes due to the restricted certainty of results.

Mortality

Overall survival

There were no usable analyses for this outcome (see Sections 2.3.1.2 as well as 2.6.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit.

Morbidity

Symptoms, recorded using the EORTC QLQ-C30 (symptom scales)

Dyspnoea, fatigue, insomnia, pain, appetite loss, diarrhoea, nausea and vomiting, constipation

No statistically significant difference between the treatment groups was shown for any of these outcomes "dyspnoea", "fatigue", "insomnia", "pain", "appetite loss", "nausea and vomiting" and "constipation". Hence, there was overall no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy for these outcomes; an added benefit is therefore not proven.

This deviates from the company's approach, which derived an indication of an added benefit for the total outcome category "morbidity".

Symptoms, recorded using the EORTC QLQ-LC13 (symptom scales)

Dysphagia

A statistically significant difference in favour of pembrolizumab + carboplatin-based chemotherapy was shown between the treatment groups for the outcome "dysphagia". This resulted in an indication of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

Dyspnoea, pain (thorax), pain (arm/shoulder), pain (other), cough, haemoptysis, alopecia, sore mouth, peripheral neuropathy

No statistically significant difference between the treatment groups was shown for each of the following outcomes: dyspnoea, pain (thorax), pain (arm/shoulder), pain (other), cough, haemoptysis, alopecia, sore mouth and peripheral neuropathy. Hence, there was overall no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy for these outcomes; an added benefit is therefore not proven.

This deviates from the company's approach, which derived an indication of an added benefit for the total outcome category "morbidity".

Health status (EQ-5D VAS)

The dossier contained no usable data for the outcome "health status" measured with the EQ-5D VAS (see Section 2.6.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "morbidity".

Health-related quality of life

EORTC QLQ-C30 (functional scales)

Physical functioning

A statistically significant difference between the treatment groups in favour of pembrolizumab + carboplatin-based chemotherapy was shown for the outcome "physical functioning". This resulted in an indication of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

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

There was no statistically significant difference between the treatment groups for the outcomes "global health status", "emotional functioning", "cognitive functioning", "role functioning" and "social functioning". Hence, there was overall no hint of an added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "health-related quality of life".

Side effects

SAEs

For the outcome "SAEs", there were no usable analyses (see Section 2.3.1.2 as well as 2.6.4.2 of the full dossier assessment). This resulted in no hint of greater or lesser harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "side effects".

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference between the treatment groups in favour of pembrolizumab + carboplatin-based chemotherapy was shown for the outcome "severe AEs (CTCAE grade

≥ 3)". This resulted in a hint of lesser harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "side effects".

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "side effects".

Immune-related AEs

A statistically significant difference between the treatment arms to the disadvantage of pembrolizumab + carboplatin-based chemotherapy was shown for the outcome "immune-related AEs". This resulted in a hint of greater harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "side effects".

Immune-related SAEs

For the outcome "immune-related SAEs", there were no usable analyses (see Section 2.3.1.2 as well as 2.6.4.2 of the full dossier assessment). This resulted in no hint of greater or lesser harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "side effects".

Immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for the outcome "immune-related severe AEs" (CTCAE grade ≥ 3). This resulted in no hint of greater or lesser harm from pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit for the total outcome category "side effects".

2.3.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present assessment:

- Age (< 65 years; ≥ 65 years)
- Sex (men, women)
- Region (EU, non-EU)
- Smoking status (active/former, never)
- Brain metastases (yes, no)
- PD-L1 expression (< 1%, ≥ 1%)
- Taxane chemotherapy (paclitaxel vs. nab-paclitaxel)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. For binary data, there must be 10 events in at least 1 subgroup.

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

Table 15 summarizes the subgroup results of pembrolizumab + carboplatin-based chemotherapy in comparison with carboplatin-based chemotherapy.

Table 15: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Study Outcome category Outcome Characteristic Subgroup	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based 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]	p-value
KEYNOTE 407						
Morbidity						
EORTC QLQ-C30 (symptom scales)[b,c]						
Pain						
Taxane chemotherapy						
Paclitaxel	84	4.63 [3.55; NC] 37 (44.0)	72	2.79 [1.38; 4.04] 47 (65.3)	0.52 [0.34; 0.81]	0.004
nab-Paclitaxel	72	4.14 [2.33; NC] 33 (45.8)	80	5.13 [3.48; NC] 33 (41.3)	1.08 [0.67; 1.76]	0.746
Total					Interaction:	0.029
EORTC QLQ-LC13 (symptom scales)[b,c]						
Pain (other)						
Sex						
Men	125	4.07 [2.92; NC] 57 (45.6)	126	4.17 [3.02; 6.24] 61 (48.4)	0.91 [0.64; 1.31]	0.621
Women	31	2.07 [1.41; 4.76] 20 (64.5)	26	NA [6.51; NC] 5 (19.2)	3.95 [1.48; 10.55]	0.006
Total					Interaction:	0.006
Alopecia						
Sex						
Men	125	0.76 [0.72; 0.95] 105 (84.0)	126	0.76 [0.72; 0.89] 105 (83.3)	0.95 [0.73; 1.25]	0.731
Women	31	0.72 [0.72; 0.85] 28 (90.3)	26	0.79 [0.72; 1.41] 20 (76.9)	2.24 [1.20; 4.18]	0.011
Total					Interaction:	0.014

(continued)

Table 15: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a] (continued)

Study Outcome category Outcome Characteristic Subgroup	Pembrolizumab + carboplatin-based chemotherapy[a]		Carboplatin-based chemotherapy[a]		Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]	
	L	Median time to event in months [95% CI] Patients with event n (%)	L	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]	p-value
Dysphagia						
Brain metastases at start of the study						
Yes	8	2.79 [0.72; 4.21] 4 (50.0)	12	NA 1 (8.3)	7.27 [0.81; 65.12]	0.076
No	148	NA 21 (14.2)	140	NA 41 (29.3)	0.42 [0.25; 0.71]	0.001
Total					Interaction:	0.013
Health-related quality of life						
EORTC QLQ-C30 (functional scales)[c,d]						
Global health status						
Region						
EU	73	6.14 [2.79; NC] 33 (45.2)	63	2.50 [1.87; 3.68] 39 (61.9)	0.61 [0.38; 0.97]	0.037
Non-EU	83	2.79 [1.64; 6.47] 47 (56.6)	89	5.13 [2.56; NC] 40 (44.9)	1.24 [0.81; 1.89]	0.328
Total					Interaction:	0.028
Social functioning						
Sex						
Men	125	4.44 [2.99; NC] 56 (44.8)	126	2.60 [2.10; 3.15] 71 (56.3)	0.68 [0.48; 0.97]	0.033
Women	31	2.09 [1.51; 5.26] 20 (64.5)	26	NA [1.41; NC] 10 (38.5)	1.81 [0.84; 3.86]	0.127
Total					Interaction:	0.023

: In combination with either paclitaxel or nab-paclitaxel.
b: Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline.
c: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 expression (TPS < 1% vs. ≥ 1%), taxane chemotherapy (paclitaxel vs. nab-paclitaxel) and region (East Asia vs. not East Asia), 2-sided p-value (Wald test).
d: Time to first deterioration; defined as decrease of the score by ≥ 10 points compared with baseline.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PD-L1: programmed cell death ligand 1; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; TPS: Tumour Proportion Score; vs.: versus

Since there are no usable subgroup analyses for the outcome "overall survival" (see Section 2.3.1.2 as well as Section 2.6.4.3.2 of the full benefit assessment), the subgroup analyses for the remaining outcomes were not conclusively interpretable either. The results of the subgroup analyses are described hereinafter, but they were not used for the derivation of the added benefit.

Morbidity

Symptoms, recorded using the EORTC QLQ-C30 (symptom scales)

Pain

There was an effect modification by the characteristic "taxane chemotherapy" for the outcome "pain". A statistically significant difference between the treatment groups in favour of pembrolizumab + carboplatin-based chemotherapy was shown for patients who had received carboplatin-based chemotherapy with paclitaxel. No difference between the treatment groups was shown for patients who had received carboplatin-based chemotherapy with nab-paclitaxel.

In the dossier, the company presented the effect modification described above, but did not use it to derive the added benefit.

Symptoms, recorded using the EORTC QLQ-LC13 (symptom scales)

Pain (other), alopecia

There was an effect modification by the characteristic "sex" for the outcomes "pain (other)" and "alopecia". A statistically significant difference between the treatment groups to the disadvantage of pembrolizumab + carboplatin-based chemotherapy was shown for women; for men there was no difference between the treatment groups.

Dysphagia

There was an effect modification by the characteristic "brain metastases at the start of the study" for the outcome "dysphagia". A statistically significant difference between the treatment groups in favour of pembrolizumab + carboplatin-based chemotherapy was shown for patients who had no brain metastases at the start of the study. For patients who had brain metastases at the start of the study, there was no difference between the treatment groups

In the dossier, the company presented the effect modifications described above, but did not use it to derive the added benefit.

Health-related quality of life

EORTC QLQ-C30 (functional scales)

Global health status

There was an effect modification by the characteristic "region" for the outcome "global health status". A statistically significant difference between the treatment groups in favour of pembrolizumab + carboplatin-based chemotherapy was shown for patients of the region "EU". For patients of the region "non-EU", there was no difference between the treatment groups.

Social functioning

There was an effect modification by the characteristic "sex" for the outcome "social functioning". A statistically significant difference between the treatment groups in favour of pembrolizumab + carboplatin-based chemotherapy was shown for men, for women there was no difference between the treatment groups.

In the dossier, the company presented the effect modifications described above, but did not use it to derive the added benefit.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. The various outcome categories and the effect sizes were taken into account. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.3.3.1 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 2.3.2 (see Table 16).

Determination of the outcome category for the outcomes on "symptoms"

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

EORTC QLQ-C30 (symptom scales): dysphagia

The dossier contains no information on the assignment of the severity category for the outcome "dysphagia" of the EORTC QLQ-C30 (symptom scales). Therefore, the outcome "dysphagia" is assigned to the outcome category "non-serious/non-severe symptoms/late complications".

Table 16: Extent of added benefit at the outcome level: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Outcome category **Outcome**	**Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	No usable analyses	Lesser benefit/added benefit not proven
Morbidity		
EORTC QLQ-C30 (symptom scales)[d]		
Dyspnoea	8.5 vs. 5.6 HR: 0.79 [0.55; 1.13]; p = 0.191	Lesser benefit/added benefit not proven
Fatigue	1.9 vs. 2.1 HR: 1.02 [0.76; 1.36]; p = 0.912	Lesser benefit/added benefit not proven
Insomnia	10.4 vs. 4.2 HR: 0.83 [0.58; 1.17]; p = 0.283	Lesser benefit/added benefit not proven
Pain	4.4 vs. 3.7 HR: 0.72 [0.52; 1.00]; p = 0.053	Lesser benefit/added benefit not proven
Appetite loss	4.0 vs. 6.2 HR: 0.99 [0.71; 1.38]; p = 0.943	Lesser benefit/added benefit not proven
Diarrhoea	NA vs. 11.3 HR: 1.07 [0.72; 1.59]; p = 0.742	Lesser benefit/added benefit not proven
Nausea and vomiting	6.4 vs. 4.2 HR: 0.98 [0.69; 1.37]; p = 0.891	Lesser benefit/added benefit not proven
Constipation	9.0 vs. 11.1 HR: 1.01 [0.70; 1.47]; p = 0.958	Lesser benefit/added benefit not proven
EORTC QLQ-LC13 (symptom scales)[d]		
Dyspnoea	2.6 vs. 2.6 HR: 0.97 [0.72; 1.31]; p = 0.836	Lesser benefit/added benefit not proven
Pain (thorax)	NA vs. 7.0 HR: 0.69 [0.46; 1.04]; p = 0.074	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	10.4 vs. 11.1 HR: 0.85 [0.58; 1.26]; p = 0.427	Lesser benefit/added benefit not proven
Pain (other)	3.6 vs. 5.7 HR: 1.10 [0.79; 1.54]; p = 0.569	Lesser benefit/added benefit not proven
Cough	NA vs. NA HR: 0.95 [0.63; 1.41]; p = 0.784	Lesser benefit/added benefit not proven
Haemoptysis	NA vs. NA HR: 0.78 [0.44; 1.39]; p = 0.402	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at the outcome level: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a] (continued)

Outcome category **Outcome**	**Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Alopecia	0.8 vs. 0.8 HR: 1.09 [0.85; 1.40]; p = 0.500	Lesser benefit/added benefit not proven
Dysphagia	NA vs. NA HR: 0.52 [0.31; 0.86]; p = 0.011 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: "minor"
Sore mouth	NA vs. NA HR: 0.83 [0.54; 1.29]; p = 0.417	Lesser benefit/added benefit not proven
Neuropathy peripheral	2.4 vs. 2.6 HR: 0.78 [0.58; 1.05]; p = 0.098	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable analyses	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (functional scales)[d]		
Global health status	3.6 vs. 3.5 HR: 0.89 [0.65; 1.23]; p = 0.488	Lesser benefit/added benefit not proven
Emotional functioning	NA vs. NA HR: 0.77 [0.52; 1.15]; p = 0.205	Lesser benefit/added benefit not proven
Cognitive functioning	4.1 vs. 3.5 HR: 0.83 [0.60; 1.16]; p = 0.277	Lesser benefit/added benefit not proven
Physical functioning	3.5 vs. 2.8 HR: 0.71 [0.52; 0.96]; p = 0.028 probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Role functioning	3.1 vs. 2.8 HR: 0.98 [0.73; 1.32]; p = 0.896	Lesser benefit/added benefit not proven
Social functioning	4.0 vs. 2.8 HR: 0.87 [0.63; 1.20]; p = 0.388	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable analyses	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at the outcome level: pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a] (continued)

Outcome category **Outcome**	**Pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Severe AEs (CTCAE grade ≥ 3)	1.9 vs. 1.2 HR: 0.69 [0.53; 0.90]; p = 0.006 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Discontinuation due to AEs	NA vs. NA HR: 1.38 [0.78; 2.44]; p = 0.274	Greater/lesser harm not proven
immune-related AEs	NA vs. NA HR: 3.09 [1.66; 5.77]; p = 0.001 HR: 0.32 [0.17; 0.60][e] probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Immune-related SAEs	No usable analyses	Greater/lesser harm not proven
Immune-related severe AEs (CTCAE grade ≥ 3)	NA vs. NA HR: 2.28 [1.00; 5.20]; p = 0.051	Greater/lesser harm not proven

a: In combination with either paclitaxel or nab-paclitaxel.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the upper limit of the confidence interval (CIu).
d: Time to confirmed deterioration.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; 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; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; SAE: serious adverse event; vs.: versus

2.3.3.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of pembrolizumab + carboplatin-based chemotherapy[a] vs. carboplatin-based chemotherapy[a]

Positive effects[b]	**Negative effects[b]**
Non-serious/non-severe symptoms/late complications ▪ dysphagia: indication of an added benefit – extent: "minor"	–
Health-related quality of life ▪ physical functioning: indication of an added benefit – extent: "minor"	–
Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "minor"	–
–	Non-serious/non-severe side effects ▪ immune-related AEs: hint of greater harm - extent: "considerable"
a: In combination with either paclitaxel or nab-paclitaxel. b: the KEYNOTE 407 study included 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. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status	

In the overall consideration of the results, there are 2 indications and 1 hint of positive effects, which are offset by 1 hint of a negative effect. Since usable analyses on overall survival are not available for the relevant subpopulation, a balancing of positive and negative effects for the overall conclusion on the added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with the ACT is not possible.

Overall, an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with carboplatin in combination with either paclitaxel or nab-paclitaxel was thus not proven for first-line treatment of patients with metastatic squamous NSCLC with a PD-L1 < 50%.

2.3.1 List of included studies

Merck Sharp & Dohme. A study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in adults with first line metastatic squamous non-small cell lung cancer (MK-3475-407/KEYNOTE-407): study details [online]. In: ClinicalTrials.gov. 19.09.2018 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02775435.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell lung cancer subjects (KEYNOTE-407) [online]. In: EU Clinical Trials Register. [Accessed: 16.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000229-38.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell Lung cancer subjects: study KEYNOTE 407 (P407V01MK3475); clinical study report [unpublished]. 2018.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell Lung cancer subjects: study KEYNOTE 407 (P407V01MK3475); Zusatzanalysen [unpublished]. 2018.

Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüs M, Mazieres J et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018; 379(21): 2040-2051.

2.4 Research question 2: patients with PD-L1 expression ≥ 50%

2.4.1 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 + carboplatin-based chemotherapy or on the ACT (status: 24 January 2019)
- bibliographical literature search on pembrolizumab + carboplatin-based chemotherapy or on the ACT (last search on 8 January 2019)
- search in trial registries for studies on pembrolizumab + carboplatin-based chemotherapy or on the ACT (last search on 9 January 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab + carboplatin-based chemotherapy or on the ACT (last search on 10 April 2019)

Concurring with the company, the check identified no relevant RCT on the comparison of pembrolizumab + carboplatin-based chemotherapy in patients with a PD-L1 expression ≥ 50% versus the ACT.

The company identified 3 studies for an adjusted indirect comparison based on RCTs. For this indirect comparison presented by the company, no additional relevant study was identified from the check of the completeness of the study pool.

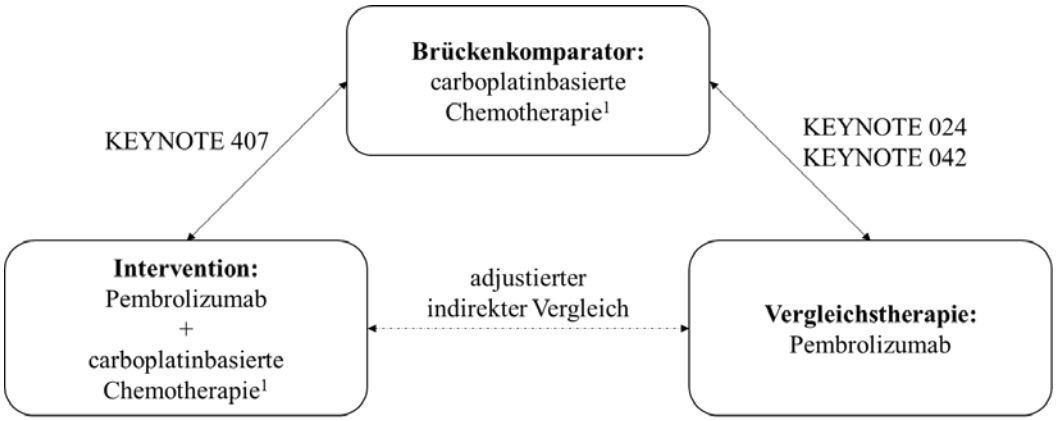
2.4.1.1 Studies included

The company presented an adjusted indirect comparison with the common comparator carboplatin-based chemotherapy for the assessment of the added benefit of pembrolizumab + carboplatin-based chemotherapy in patients with PD-L1 expressions ≥ 50% . The company justified the choice of the common comparator with the fact that it had identified RCTs which investigated the same common comparator (a carboplatin-based chemotherapy) for pembrolizumab + carboplatin-based chemotherapy (which was to be compared) as well as for the ACT “pembrolizumab (monotherapy)” in the relevant field of application. Concurring with the company’s assessment, carboplatin-based chemotherapy is considered the only option for an adjusted indirect comparison via an adequate common comparator. The studies listed in the following Table 18 were included in the benefit assessment.

Table 18: Study pool – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)
Intervention vs. common comparator			
KEYNOTE 407	Yes	Yes	No
ACT vs. common comparator			
KEYNOTE 024	Yes	Yes	No
KEYNOTE 042	Yes	Yes	No
a: In combination with either paclitaxel or nab-paclitaxel. b: Study sponsored by the company. ACT: appropriate comparator therapy; RCT: randomized controlled trial; vs.: versus			

Figure 1 shows a schematic representation of the indirect comparison.



1: In combination with either paclitaxel or nab-paclitaxel.

Brückenkomparator: common comparator; Carboplatinbasierte Chemotherapie: carboplatin-based chemotherapy; Intervention: intervention; Adjustierter indirekter Vergleich: adjusted indirect comparison; Vergleichstherapie: comparator therapy

Figure 1: Study pool for the indirect comparison between pembrolizumab + carboplatin-based chemotherapy and the ACT pembrolizumab

The KEYNOTE 024 study was already known from the dossier assessment on A17-06 [9], where it is described in detail. Only a subpopulation of 6 patients is relevant for the benefit assessment in the present research question. However, 108 patients from the KEYNOTE 407 study and 120 patients from the KEYNOTE 042 study were included in the indirect comparison.

Due to the low number of patients from the KEYNOTE 024 study, the company excluded these patients from the indirect comparison. This approach is adequate. The KEYNOTE 024 study was not used for the indirect comparison and is not presented hereinafter.

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 19 and Table 20 describe the studies used for the benefit assessment.

Table 19: Characteristics of the studies included – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcomes; secondary outcomes[b]
Intervention vs. common comparator						
KEYNOTE 407	RCT, double-blind, parallel	Adult patients with histologically or cytologically confirmed stage IV squamous[c] NSCLC, ECOG ≤ 1 and without prior systemic treatment[d]	▪ Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (n = 278) ▪ Carboplatin and either paclitaxel or nab-paclitaxel (N = 281) Relevant subpopulation thereof[e]: ▪ Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (n = 55) ▪ Carboplatin and either paclitaxel or nab-paclitaxel (n = 53)	▪ Screening: 28 days prior to the start of treatment ▪ Treatment: Until complete response or until progression, unacceptable toxicity, occurrence of intercurrent diseases that make further treatment impossible, pregnancy, discontinuation of treatment due to decision by the physician or the patient or after a maximum of 35 cycles of pembrolizumab[f] ▪ Follow-up[g]: at most until death	125 centres in Australia, Canada, China, Germany, France, Italy, Japan, Mexico, Poland, Russia, South Korea, Spain, Thailand, The Netherlands, Turkey, Hungary and the United States 08/2016–ongoing Data cut-off: 3 April 2018	Primary: overall survival PFS Secondary: morbidity, health-related quality of life, AEs

(continued)

Table 19: Characteristics of the studies included – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab (continued)

Study	Study design	Population	▪ Interventions (number of randomized patients)	▪ Study duration	Location and period of study	Primary outcomes; secondary outcomes[b]
ACT vs. common comparator						
KEYNOTE 042	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed with locally advanced or metastatic NSCLC, PD-L1 expressing tumours (TPS ≥ 1%) without EGFR mutations or ALK translocations, ECOG ≤ 1, no previous systemic therapy[d]	▪ Pembrolizumab (N = 637) ▪ Platinum-based chemotherapy[h] (n = 637) Relevant subpopulation thereof[e,i]: ▪ Pembrolizumab (n = 57) ▪ Carboplatin-based chemotherapy (n = 63)	▪ Screening: 30 days prior to the start of treatment ▪ Treatment: until progression, unacceptable side effects, study discontinuation due to decision by the physician or the patient, complete response or a maximum of 35 cycles of pembrolizumab[f] Follow-up: outcome-specific[g], at most until death	196 centres in 32 countries: Argentina, Brazil, Bulgaria, Canada, Columbia, Czech Republic, Chile, China, Estonia, Guatemala, Hong Kong, Hungary, Japan, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, Vietnam 11/2014–ongoing First data cut-off: 26 February 2018 Second data cut-off: final PFS analysis: 4 September 2018	Primary: overall survival Secondary: AE

(continued)

Table 19: Characteristics of the studies included – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab (continued)

a: In combination with either paclitaxel or nab-paclitaxel.
b: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
c: Patients with mixed histology could be included in the study if the sample comprised squamous components.
d: Patients with prior neoadjuvant or adjuvant treatment had to have received their last treatment at least 12 month (KEYNOTE 407) or at least 6 months (KEYNOTE 42) before diagnosis of the metastatic disease.
e: The relevant subpopulation comprised patients with PD-L1 expressing tumours (TPS ≥ 50%) who had been treated in accordance with the criteria of the pharmaceutical directive for off-label use (Appendix VI to Section K [3]) of carboplatin (TPC subpopulation).
f: Patients in the intervention arm could temporarily discontinue treatment after complete and confirmed response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab as monotherapy at the investigator's discretion ("second course phase") after subsequent confirmed progression (if certain conditions regarding treatment duration and disease status were met).
g: Outcome-specific information is provided in Table 21.
h: Within the framework of the chemotherapy, the following platinum-based combination chemotherapies were selected on an individual basis prior to randomization: carboplatin + pemetrexed and carboplatin + paclitaxel.
i: The relevant subpopulation comprised patients with metastatic NSCLC and squamous histology as well as patients assigned to the platinum-based combination chemotherapy carboplatin + paclitaxel.

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; n: relevant subpopulation; EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomized (included) patients; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; TPC: treatment of physician's choice; TPS: Tumour Proportion Score; vs.: versus

Table 20: Characteristics of the interventions – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

Study	Intervention/comparator therapy	Common comparator
Intervention vs. common comparator		
KEYNOTE 407	see data in Table 7	
ACT vs. common comparator		
KEYNOTE 042	Pembrolizumab 200 mg IV (infusion administered over 30 minutes) every 3 weeks for a maximum of 35 cycles	6 cycles of carboplatin-based combination chemotherapy[b]: ▪ Carboplatin AUC 5 or 6 mg/mL/min administered as IV infusion over 30 to 60 minutes, every 3 weeks) ▪ Paclitaxel 200 mg/m² IV, as infusion administered over 3 hours, every 3 weeks
	Dose adjustments in case of toxicities ▪ Allowed for carboplatin and paclitaxel in line with the SPC ▪ Not allowed for pembrolizumab (treatment could be discontinued) **Pretreatment** ▪ Adjuvant or neoadjuvant therapy, the last treatment had to be administered at least 6 months prior to the development of the metastatic disease **Non-permitted pretreatment** ▪ Systemic treatment of stage IIIB and IV NSCLC **Non-permitted concomitant treatment** ▪ Other chemotherapies or immunotherapies ▪ Surgery for symptom and tumour control ▪ Radiotherapy ▪ Live vaccines ▪ Corticosteroids except for the treatment of AEs or used as premedication of a chemotherapy used in the study ▪ Bisphosphonates and/or RANKL inhibitors[c]	

a: In combination with either paclitaxel or nab-paclitaxel.
b: Within the framework of the chemotherapy, the following platinum-based combination chemotherapies were selected on an individual basis prior to randomization: carboplatin + pemetrexed and carboplatin + paclitaxel. For the indirect comparison, the study population of KEYNOTE 042 was limited to patients selected for carboplatin-based chemotherapy with paclitaxel and to patients with squamous histology in the metastatic stage.
c: In the study, continuation of these therapies was only allowed for patients whose treatment had started prior to study inclusion.
AE: adverse event; AUC: area under the curve; IV: intravenous; NSCLC: non-small cell lung cancer; RANKL: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; vs.: versus

Study design

Study with the intervention: KEYNOTE 407

The KEYNOTE 407 study is also used to assess the added benefit of research question 1 (patients with PD-L1 expression < 50%); a description of the study design can be found in Section 2.3.1.2 of the present dossier assessment.

Study with the ACT: KEYNOTE 042

KEYNOTE 042 is an ongoing, randomized, open-label, controlled parallel-group study. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. A total of 1274 patients were randomly allocated to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637) in a 1:1 ratio. Randomization was stratified by ECOG-PS (0/1), histology (squamous, non-squamous), PD-L1 expression (1–49%/≥ 50%) and geographical region (East Asia/not East Asia). The study included adults with histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC, whose tumours expressed PD-L1 ≥ 1%. Prior systemic treatment was not allowed in the studies. For patients who had received adjuvant or neoadjuvant therapy, treatment had to be terminated at least 6 months prior to the development of metastases. The ECOG-PS had to be 0 or 1 in the included patients. Patients with active brain metastases were excluded from the study. The treatment option (carboplatin + paclitaxel or carboplatin + pemetrexed) suitable for the patient in case of randomization to the comparator arm was specified by an investigator on an individual basis prior to randomization.

In the study, the PD-L1 expression of the tumour tissue was determined by means of the Dako Commercial Ready Assay (monoclonal, PD-L1-targeted, antibody of the 22C3 clone) using immunohistochemistry. In doing so, the Tumour Proportion Score (TPS) was determined, which indicates the percentage of the live tumour cells whose membranes are partially or completely stained. Unless stated otherwise, the specified PD-L1 expression refers to the analyses with TPS in the present dossier assessment.

Patients in the intervention arm received pembrolizumab in accordance with the SPC [6,7]. The maximum treatment duration was 35 cycles. Patients in the control arm received carboplatin in accordance with the SPC [5] or the pharmaceutical directive for off-label use (Appendix VI to Section K [3]). Neither the SPC [8] nor the pharmaceutical directive on off-label use (Appendix VI to Section K [3]) contains information on the dosage of paclitaxel in combination with carboplatin. In the study, paclitaxel was administered as 3-hour infusion at a dosage of 200 mg/m² body surface area. Patients in the comparator arm received 6 cycles of the carboplatin-based chemotherapy.

“Overall survival” was the primary outcome of the study. Patient-relevant secondary outcomes were AEs.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation due to decision by the physician or the patient. Treatment in the intervention arm was generally restricted by the maximum number of allowed cycles of pembrolizumab. According to the study documents, it must be assumed that only very few included patients received the maximum number of pembrolizumab cycles.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. There were no restrictions

regarding the type of subsequent therapy. The study design did not intend a switch of treatment from the ACT to pembrolizumab monotherapy after disease progression. At the time point of the data cut-off of 26 February 2018, the proportion of patients with antineoplastic subsequent therapy in the subpopulation was 37.7% in the intervention arm and 44.0% in the comparator arm (see Table 35 of the full dossier assessment). In the comparator arm, 28 (4.4%) patients had switched to monotherapy with pembrolizumab.

Implementation of the Pharmaceutical Directive on the use of carboplatin

As already explained for research question 1 (patients with PPD-L1 expression < 50%) in Section 2.3.1.2, the criteria of Appendix IV to Section K of the Pharmaceutical Directive [3] must be considered in carboplatin treatment. Neither for the KEYNOTE 407 study nor for the KEYNOTE 042 study, treatment with carboplatin-based chemotherapy was explicitly limited according to the criteria of the Pharmaceutical Directive. Therefore, the company conducted retrospective interviews with the investigators (referred to as TPC interview by the company), as it had done for research question 1. For this purpose, the investigator was to justify the decision for treatment with a carboplatin-based combination chemotherapy on an individual basis.

In its dossier, the company provided partially unclear information on the reasons for the allocation of the patients to carboplatin-based chemotherapy. Therefore, a slight uncertainty remains whether all points of the specifications stipulated in the Pharmaceutical Directive for off-label use were completely implemented (see Section 2.6.4.1 of the full dossier assessment). However, it was assumed that the patients of the TPC population essentially met the criteria of the pharmaceutical directive for the off-label use (Appendix VI to Section K [3]) of carboplatin in the present therapeutic indication.

Subpopulation of the studies relevant for the research question

The present research question includes patients with metastatic squamous NSCLC and PD-L1 expression ≥ 50%, who had moreover received treatment with carboplatin in accordance with the criteria of the pharmaceutical directive for off-label use (Appendix VI to Section K [3]).

Patients with metastatic squamous NSCLC

The present therapeutic indication comprised patients with metastatic squamous NSCLC. The KEYNOTE 042 study included patients with squamous and non-squamous NSCLC as well as patients with stage IIIB and IV disease. For the relevant subpopulation, the company only considered patient populations with metastatic (stage IV) squamous NSCLC.

PD-L1 expression ≥ 50%

The patient population with a PD-L1 expression ≥ 50% is relevant for the present research question. The KEYNOTE 407 study included patient irrespective of the PD-L1 expression. However, KEYNOTE 042 included patients with a PD-L1 expression ≥ 1%. The company

considered the patient population with PD-L1 expression ≥ 50% to be the relevant subpopulation.

Patients treated in accordance with the criteria of the pharmaceutical directive on the use of carboplatin

As described above, patients were to be treated in accordance with the criteria of Appendix VI to Section K of the pharmaceutical directive [3] on the use of carboplatin. For this purpose, the company conducted a retrospective TPC interview. As a result, it is possible to use a subpopulation of each study that includes patients treated in accordance with the criteria of the pharmaceutical directive (referred to as the TPC survey population by the company, see Section 2.3.1.2).

Common comparator consisting of carboplatin in combination with either paclitaxel or nab-paclitaxel

Carboplatin-based chemotherapy in combination with either paclitaxel or nab-paclitaxel is the only suitable common comparator for an adjusted indirect comparison with the studies KEYNOTE 407 and KEYNOTE 042. In the KEYNOTE 042 study, further platinum-based combination chemotherapies could be administered besides carboplatin + paclitaxel. For the relevant subpopulation, the company considered only those patients who received carboplatin + paclitaxel as treatment option.

Summary

For the studies KEYNOTE 407 and KEYNOTE 042, the company presented analyses of the subpopulations who met the criteria described above. In the KEYNOTE 407 study, these were N = 55 patients in the intervention arm and N = 53 patients in the comparator arm. In the KEYNOTE 042 study, N = 57 patients were included in the intervention arm and N = 63 patients were included in the comparator arm. The analyses presented by the company represent the subpopulation relevant for the present research question.

Data cut-offs

KEYNOTE 407

As was the case for research question 1 (see Section 2.3.1.2), the company presented analyses of the pre-specified data cut-off of 3 April 2018 for the KEYNOTE 407 study. These were used for the present research question.

KEYNOTE 042

The company used the second interim analysis of the KEYNOTE 042 study conducted about 38 months after the start of the study on 26 February 2018 and justified this chiefly with the fact that these data had also been submitted to the EMA. Although the company presented the final analysis performed about 45 months after the start of the study on 4 September 2018 as supplementary information, it did not conduct an indirect comparison with the effect estimations. The analyses based on the data cut-off of 26 February 2018 were used for the

benefit assessment, since the analyses of the data cut-off of 4 September 2018 on the indirect comparison were not completely available.

Follow-up

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

Table 21: Planned duration of follow-up observation – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE 407	see data in Table 8
KEYNOTE 042	
Mortality	
Overall survival	▪ At the end of treatment (except for progression): every 3 months until progression or initiation of new antineoplastic treatment ▪ After progression or initiation of a new antineoplastic treatment: every 2 months until death
Morbidity	Not recorded
Health-related quality of life	Not recorded
Side effects	
AEs	▪ Until 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first)
SAEs and immune-related AEs	▪ Until 90 days after the last study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment is initiated, whichever occurred first)

a: In combination with either paclitaxel or nab-paclitaxel.

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-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

In the KEYNOTE 407 and the KEYNOTE 042 studies, the observation periods for the outcomes “morbidity”, “health-related quality of life” (if recorded) and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 or 90 days). 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”.

Patient characteristics

Table 22 shows the characteristics of the patients in the studies included.

Table 22: Characteristics of the study populations – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

Study Characteristics Category	KEYNOTE 407		KEYNOTE 042	
	Pembrolizumab + carboplatin-based chemotherapy[a]	Carboplatin-based chemotherapy[a]	Pembrolizumab	Carboplatin-based chemotherapy[b]
	N[c] = 55	N[c] = 53	N[c] = 57	N[c] = 63
Age [years], mean (SD)	65 (8)	65 (9)	64 (9)	63 (8)
Sex [F/M], %	21.8/78.2	20.8/79.2	19.3/80.7	20.6/79.4
Ethnicity, n (%)				
White	44 (80.0)	43 (81.1)	42 (73.7)	47 (74.6)
Non-white	11 (20.0)[d,e]	10 (18.9)[d,e]	15 (26.3)	16 (25.4)
Unknown	–	–	–	–
Region, n (%)				
EU	19 (34.5)	23 (43.4)	20 (35.1)	12 (19.0)
Non-EU	36 (65.5)	30 (56.6)	37 (64.9)	51 (81.0)
Smoking status, n (%)				
Never-smoker	6 (10.9)	7 (13.2)	7 (12.3)	8 (12.7)
Former	33 (60.0)	38 (71.7)	33 (57.9)	35 (55.6)
Active	16 (29.1)	8 (15.1)	17 (29.8)	20 (31.7)
ECOG PS, n (%)				
0	9 (16.4)	16 (30.2)	14 (24.6)	15 (23.8)
1	46 (83.6)	37 (69.8)	43 (75.4)	48 (76.2)
Disease stage, n (%)				
IV	55 (100.0)	53 (100.0)	57 (100.0)	63 (100.0)
Metastases, n (%)	ND[f]	ND[f]	ND[f]	ND[f]

(continued)

Table 22: Characteristics of the study populations – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab (continued)

Study Characteristics Category	KEYNOTE 407		KEYNOTE 042	
	Pembrolizumab + carboplatin-based chemotherapy[a]	Carboplatin-based chemotherapy[a]	Pembrolizumab	Carboplatin-based chemotherapy[b]
	N[c] = 55	N[c] = 53	N[c] = 57	N[c] = 63
Time since initial diagnosis [months]				
Mean (SD)	5.1 (10.3)	6.9 (14.0)	2.2 (3.0)	3.3 (6.0)
Median [min; max]	1.4 [0.2; 50.2]	1.6 [0.2; 62.5]	1.4 [0.5; 20.5]	1.3 [0.5; 39.3]
Tumour size at start of the study [mm]				
Mean (SD)	113.4 (85.7)[g]	111.3 (69.8)[g]	118.4 (57.1)	133.8 (69.5)
Median [min; max]	85.4 [23.8; 424.3]	90.6 [10.3; 275.9]	106.4 [29.9; 241.4]	119.8 [19.2; 394.3]
Brain metastases, n (%)				
Yes	6 (10.9)	6 (11.3)	2 (3.5)	2 (3.2)
No	49 (89.1)	47 (88.7)	55 (96.5)	61 (96.8)
Prior therapies, n (%)	Adjuvant/neoadjuvant prior therapy:			
Adjuvant prior therapy	2 (3.6)	1 (1.9)	1 (1.8)	1 (1.6)
Neoadjuvant prior therapy			0 (0.0)	1 (1.6)
Taxane-based chemotherapy, n (%)				
Carboplatin + paclitaxel	33 (60.0)	28 (52.8)	57 (100.0)	63 (100.0)
Carboplatin + nab-paclitaxel	22 (40.0)	25 (47.2)	0 (0.0)	0 (0.0)
Treatment discontinuation, n (%)	ND[h]	ND[h]	ND[h]	ND[h]
Study discontinuation, n (%)	ND[h]	ND[h]	ND[h]	ND[h]

(continued)

Table 22: Characteristics of the study populations – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab (continued)

a: In combination with either paclitaxel or nab-paclitaxel.
b: In combination with paclitaxel.
c: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
d: "Non-white" includes Native Americans or Native Alaskans, Asians, Black or African Americans and Native Hawaiians or Native Pacific Islanders.
e: Institute's calculation.
f: Data on stage M1, M1A, M1B and MX tumour metastases are not available for the relevant subpopulation.
g: The data of 54 patients (in the intervention arm) or 53 patients (in the comparator arm) were considered in the calculation.
h: There was no information on treatment and study discontinuations for the relevant subpopulation.
F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and clinical characteristics of the patients were balanced between the study arms of the studies KEYNOTE 407 and KEYNOTE 042 and sufficiently similar between the studies. In both studies, the mean age of the majority of the patients included in the relevant subpopulation was 64 years, the majority were male, most of them were white. One third of the patients were from the EU. At the start of the study, the majority of the patients had an ECOG-PS of 1 and no brain metastases. Median initial diagnosis was 1.4 months ago.

Differences between the two studies were shown in the common comparator: In both studies, patients in the comparator arm received carboplatin. Moreover, 47% of the patients in the relevant subpopulation of the KEYNOTE 407 study received nab-paclitaxel and 53% received paclitaxel. In the KEYNOTE 042 study, all patients of the relevant subpopulation in the comparator arm received paclitaxel. The difference must be considered to be critical particularly because of the differences in the side effect profile of carboplatin in combination with paclitaxel versus carboplatin in combination with nab-paclitaxel described in the literature [10]. At the same time, the subgroup analyses of the KEYNOTE 407 study showed no effect modification by the type of taxane in research question 1 of the present benefit assessment, with the exception of the symptom “pain” (see Section 2.3.2.4). Patients in the comparator arm of the KEYNOTE 407 study received carboplatin-based chemotherapy for a total of 4 cycles, whereas patients in the KEYNOTE 042 study received 6 cycles. For the present benefit assessment, it is examined for the specific outcomes whether there are relevant differences in the results of the common comparators.

Course of the study

Table 23 shows the mean and median treatment duration of the patients and the mean and median observation period for individual outcomes.

Table 23: Data on the course of the study – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + carboplatin-based chemotherapy[a]**	**Carboplatin-based chemotherapy[a]**
Intervention vs. common comparator		
KEYNOTE 407	N = 55	N = 53
Treatment duration [months]		
Median [min; max]	5.6 [0.0; 14.4]	3.2 [0.0; 17.9]
Mean (SD)	5.8 (3.8)	3.8 (3.4)
Observation period [months]		
Overall survival		
Median [min; max]	8.1 [0.4; 14.7]	5.9 [0.1; 18.1]
Mean (SD)	8.2 (3.8)	6.7 (4.5)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (SAEs)	No usable data	
Study **Duration of the study phase** **Outcome category**	**Pembrolizumab**	**Carboplatin-based chemotherapy[a]**
ACT vs. common comparator		
KEYNOTE 042	N = 57	N = 61
Treatment duration [months]		
Median [min; max]	6.3 [0.0; 27.3]	3.5 [0.0; 26.8]
Mean (SD)	8.1 (7.8)	3.3 (3.3)
Observation period [months]		
Overall survival		
Median [min; max]	13.6 [0.3; 34.5]	8.8 [0.2; 29.2]
Mean (SD)	13.3 (9.2)	10.2 (6.5)
Morbidity	Data not recorded	
Health-related quality of life	Data not recorded	
Side effects (SAEs)		
Median [min; max]	9.2 [0.3; 30.3]	6.4 [0.4; 29.7]
Mean (SD)	10.6 (8.2)	6.0 (3.5)

a: In combination with either paclitaxel or nab-paclitaxel.
ASaT: All Subjects as Treated; max: maximum; min: minimum; N: number of analysed patients (ASaT); ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

In the studies KEYNOTE 407 and KEYNOTE 042, treatment duration in the intervention arm is clearly longer than in the comparator arm. Treatment duration in the intervention and comparator arms is very similar between the studies.

The observation period for the outcome “overall survival” is also clearly longer in the intervention arms of both studies. The observation period for the outcome “overall survival” in both study arms is longer in the KEYNOTE 042 study than in the study KEYNOTE 407.

The data on the observation period of SAEs provided by the company in Module 4 C are not interpretable, since patients who switched from the control arm to monotherapy with pembrolizumab were only considered until the time point of the treatment switch (see Section 2.3.1.2 as well as Section 2.6.4.2 of the full dossier assessment).

For the intervention and comparator arms, information on the observation periods is lacking for the outcomes “morbidity”, “health-related quality of life” as well as for further outcomes of the category “side effects”. It was assumed, however, that for these outcomes the difference in the observation period between the study arms was similar to the difference in treatment duration, because the follow-up observation was limited (see Table 8 for the planned follow-up observation).

Summary of the similarities of the studies in the adjusted indirect comparison

The assumption of similarity for the indirect comparison did not have to be discarded due the described differences between the studies KEYNOTE 407 and KEYNOTE 042 (administration of paclitaxel/nab-paclitaxel, different number of cycles of the carboplatin-based chemotherapy) regarding the common comparator. However, potential impacts of these differences have to be investigated for the individual outcomes.

Switch of treatment from the comparator arm to monotherapy with pembrolizumab after disease progression

After confirmed disease progression and suitability, patients in the KEYNOTE 407 study could switch from the comparator arm to monotherapy with pembrolizumab in line with the protocol. These treatments are approved in the corresponding line of treatment [6,7]. In the KEYNOTE 042 study, however, a treatment switch to monotherapy with pembrolizumab was not stipulated in line with the protocol. However, there were no limitations with regard to subsequent therapies. According to the study documents, relevant proportions of the patients from the KEYNOTE 042 study had switched to various subsequent therapies at the data cut-off of 26 February 2018 (see above in the Section on the details of the KEYNOTE 042 study).

In Module 4 C of its dossier, the company indicates the number of patients who had switched from the comparator arm to monotherapy with pembrolizumab for both studies. In the KEYNOTE 407 study, the proportion of patients was 24.5% (n = 13) in the relevant subpopulation; in KEYNOTE 042, it was 11.1% (n = 7) at the time point of the data cut-off on 3 April 2018. Moreover, the company presented Kaplan-Meier curves for the time to treatment switch (Figures 12 and 13 in Appendix A of the full dossier assessment). The figures show that the majority of these treatment switches took place in the period between 3 and 12 months. Overall, high proportions of the patients who switched from the control arm to monotherapy with pembrolizumab thus switched treatment at an early stage.

Methods used for the analysis of the outcome on overall survival in the relevant subpopulation unclear

The analyses of the outcome "overall survival" presented by the company were not interpretable due to contradictory information provided by the company. This is explained below:

When describing the operationalization of the outcome "overall survival" for the studies KEYNOTE 407 and KEYNOTE 042, the company stated in Module 4 C of its dossier that only patients who had switched from the control arm to monotherapy with pembrolizumab were censored in the statistical analyses at the time point of the treatment switch. In the study documents of the KEYNOTE 407 and the KEYNOTE 042 studies, "overall survival" was operationalized as period between randomization and death for any reason. The analysis on "overall survival" planned primarily in the studies is an ITT analysis. Accordingly, the result tables in Module 4 C on the ITT analyses indicate that the observation was censored at the time point of the data cut-off. This is contrary to the data of the operationalization.

Altogether, the data on the analyses of the outcome "overall survival" are contradictory. The results presented by the company are therefore not usable. Meaningful interpretation requires an ITT analysis with censoring at the time point of the last observation or the data cut-off.

Risk of bias across outcomes (study level)

Table 24 shows the risk of bias across outcomes (risk of bias at study level).

Table 24: Risk of bias across outcomes (study level) – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

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			
Intervention vs. common comparator							
KEYNOTE 407	Yes	Yes	Yes	Yes	Yes	Yes	Low
ACT vs. common comparator							
KEYNOTE 042	Yes	Yes	No	No	Yes	Yes	Low

a: In combination with either paclitaxel or nab-paclitaxel.
RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for both studies. This concurs with the company's assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.4.3.2 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and QLQ-LC13
  - health status, measured using the EQ-5D VAS
- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - immune-related AEs, SAEs and severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 C) (see Section 2.6.4.3.2 of the full dossier assessment).

Table 25 shows for which outcomes data were available in the studies included.

Table 25: Matrix of the outcomes – RCT, indirect comparison: pembrolizumab + carboplatin-based chemotherapy[a] vs. pembrolizumab

Study	Outcomes										
	Overall survival	Symptoms (EORTC QLQ-C30 and QLQ-LC13)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-LC13)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Immune-related AEs	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Further specific AEs
Intervention vs. common comparator											
KEYNOTE 407	No[b]	Yes	No[b]	Yes	No[b]	Yes	Yes	Yes	No[b]	Yes	No[b]
ACT vs. common comparator											
KEYNOTE 042	No[b]	No[c]	No[c]	No[c]	No[b]	Yes	Yes	No[b]	No[b]	No[b]	No[b]

a: In combination with either paclitaxel or nab-paclitaxel.
b: No usable data available; see Sections 2.4.1.2 as well as Sections 2.6.4.2 and 2.6.5.3.2 of the full dossier assessment.
c: Outcome not recorded.

ACT: appropriate comparator therapy; 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; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Usable data for the indirect comparison are not available for the outcomes “overall survival”, “symptoms”, “health status”, “health-related quality of life”, “SAEs”, “immune-related AEs”, “immune-related SAEs”, “immune-related severe AEs (CTCAE grade ≥ 3)” and potentially further specific AEs (for reasons, see Sections 2.4.1.2 as well as 2.6.4.2 and 2.6.5.3.2 of the full dossier assessment).

2.4.2.2 Results

Overall consideration of the available data results in the following picture:

There are no usable data for the outcomes of the categories “mortality”, “morbidity” and “health-related quality of life”; some of the outcomes were not recorded in the studies. For the outcomes of the category “side effects”, usable analyses were only available for the outcomes “discontinuation due to AEs” and “severe AEs (CTCAE grade ≥ 3)”. There are no usable data for the outcomes “SAEs”, “immune-related AEs”, “immune-related SAEs” and “immune-related severe AEs” (CTCAE grade ≥ 3). Therefore, the present data situation does not permit

a benefit assessment with subsequent weighing of positive and negative effects despite the general suitability of the studies KEYNOTE 407 and KEYNOTE 042 for the indirect comparison. Overall, the data on the indirect comparison presented by the company are unsuitable to derive an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel versus pembrolizumab in first-line treatment of metastatic squamous NSCLC with a PD-L1 expression ≥ 50% in adults. This resulted in no hint of an added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with pembrolizumab; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

An added benefit is not proven, since the company presented no suitable data for the assessment of the added benefit of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel in comparison with pembrolizumab in the first-line treatment of adults with metastatic squamous NSCLC with a PD-L1 expression ≥ 50%.

2.4.4 List of included studies

KEYNOTE 042

Merck Sharp & Dohme. A randomized, open label, phase III study of overall survival comparing pembrolizumab (MK-3475) versus platinum based chemotherapy in treatment naïve subjects with PD-L1 positive advanced or metastatic non-small cell lung cancer: study KEYNOTE 042 (P042V02MK3475); Zusatzanalysen [unpublished]. 2018.

Merck Sharp & Dohme. A randomized, open label, phase III study of overall survival comparing pembrolizumab (MK-3475) versus platinum based chemotherapy in treatment naïve subjects with PD-L1 positive advanced or metastatic non-small cell lung cancer: study KEYNOTE 042 (P042V02MK3475); clinical study report [unpublished]. 2018.

Merck Sharp & Dohme. A randomized, open label, phase III study of overall survival comparing pembrolizumab (MK-3475) versus platinum based chemotherapy in treatment naïve subjects with PD-L1 positive advanced or metastatic non-small cell lung cancer (Keynote 042) [online]. In: EU Clinical Trials Register. [Accessed: 16.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001473-14.

Merck Sharp & Dohme. Study of pembrolizumab (MK-3475) versus platinum-based chemotherapy for participants with programmed cell death-ligand 1 (PD-L1)-positive advanced or metastatic non-small cell lung cancer (MK-3475-042/KEYNOTE-042): study details [online]. In: ClinicalTrials.gov. 15.03.2019 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02220894.

KEYNOTE 407

Merck Sharp & Dohme. A study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in adults with first line metastatic squamous non-small cell lung cancer (MK-3475-407/KEYNOTE-407): study details [online]. In: ClinicalTrials.gov. 19.09.2018 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02775435.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell lung cancer subjects (KEYNOTE-407) [online]. In: EU Clinical Trials Register. [Accessed: 16.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000229-38.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell Lung cancer subjects: study KEYNOTE 407 (P407V01MK3475); clinical study report [unpublished]. 2018.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic squamous non-small cell Lung cancer subjects: study KEYNOTE 407 (P407V01MK3475); Zusatzanalysen [unpublished]. 2018.

Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüs M, Mazieres J et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018; 379(21): 2040-2051.

2.5 Probability and extent of added benefit – summary

Table 26 summarizes the result of the assessment of the added benefit of pembrolizumab + carboplatin-based chemotherapy in comparison with the ACT.

Table 26: Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel – Probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression < 50%	Cisplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel) *or* **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or **paclitaxel**; see also Appendix VI to Section K of the pharmaceutical directive [3]) *or* **carboplatin in combination with nab-paclitaxel**	Added benefit not proven
2	First-line treatment of metastatic squamous NSCLC in adults[b] with a PD-L1 expression ≥ 50%	Pembrolizumab as monotherapy	Added benefit not proven

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: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to the IASLC and the UICC), without medical indication for definitive local therapy.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; UICC: Union for International Cancer Control

The assessment described above deviates from that of the company, which derived an indication of a major added benefit for patients with a PD-L1 expression < 50% (research question 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.

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. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. 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 2015; 58(1): 43-58.

3. Gemeinsamer Bundesausschuss. Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie: Verordnungsfähigkeit von zugelassenen Arzneimittel in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use) [online]. 26.03.2019 [Accessed: 13.05.2019]. URL: https://www.g-ba.de/downloads/83-691-524/AM-RL-VI-Off-label-2019-03-26.pdf.

4. Celgene. Abraxane 5 mg/ml Pulver zur Herstellung einer Infusionssuspension: Fachinformation [online]. 07.2018 [Accessed: 24.04.2019]. URL: https://www.fachinfo.de/.

5. Fresenius Kabi. Carboplatin Kabi 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 06.2018 [Accessed: 24.04.2019]. URL: https://www.fachinfo.de/.

6. MSD. Keytruda 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 03.2019 [Accessed: 24.04.2019]. URL: https://www.fachinfo.de/.

7. MSD. Keytruda 50 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 03.2019 [Accessed: 24.04.2019]. URL: https://www.fachinfo.de/.

8. Fresenius Kabi. Paclitaxel Kabi 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 11.2016 [Accessed: 24.04.2019]. URL: https://www.fachinfo.de/.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (nicht kleinzelliges Lungenkarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-06 [online]. 10.05.2017 [Accessed: 18.05.2017]. (IQWiG-Berichte; Volume 509). URL: https://www.iqwig.de/download/A17-06_Pembrolizumab_Nutzenbewertung-35a-SGB-V.pdf.

10. Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol 2012; 30(17): 2055-2062.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-31-pembrolizumab-squamous-non-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.11927.html.