IQWiG Reports – Commission No. A19-30

Pembrolizumab (non-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 (nicht 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Pembrolizumab (non-squamous NSCLC, combination chemotherapy) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

29 March 2019

Internal Commission No.:

A19-30

Address of publisher:

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

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

Medical and scientific advice:

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment:

- Vanessa Voelskow
- Lars Beckmann
- Judith Gibbert
- Petra Kohlepp
- Inga Overesch
- Dominik Schierbaum
- Ulrike Seay
- Beate Wieseler

Keywords: pembrolizumab, pemetrexed, carboplatin, cisplatin, carcinoma – non-small-cell lung, benefit assessment, NCT02039674, NCT02578680, NCT02142738, NCT02220894

Table of contents

List of tables[2]

Page

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

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
CTCAE	Common Terminology Criteria for Adverse Events
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	European Quality of Life Questionnaire 5 Dimensions
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	Medicinal Dictionary for Regulatory Activities
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PT	Preferred Term
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
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TPC	treatment of physician's choice
TPS	Tumour Proportion Score
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab in combination with pemetrexed and platinum-based chemotherapy. 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 pemetrexed and platinum-based chemotherapy as first-line treatment in comparison with the appropriate comparator therapy (ACT) in adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-positive tumour mutations.

The research questions presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy

Research question	Subindication	ACT[a]
1	First-line treatment of metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with a PD-L1 expression < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see also Appendix VI to Section K of the Pharmaceutical Directive *or* ▪ carboplatin in combination with nab-paclitaxel
2	First-line treatment of the metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression ≥ 50%[b]	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: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The company followed the G-BA's specification of the ACT for both research questions and chose a platinum-based combination chemotherapy consisting of either cisplatin or carboplatin each in combination with pemetrexed from the options presented for research question 1.

In the present assessment, the following terms are used for the drug under assessment and the ACT chosen by the company:

- Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy: pembrolizumab + platinum-based chemotherapy
- Cisplatin or carboplatin in combination with pemetrexed: platinum-based chemotherapy

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 cell death ligand 1 (PD-L1) expression < 50%

Study pool and study characteristics

The studies KEYNOTE 021G and KEYNOTE 189 were used for the benefit assessment of pembrolizumab + platinum-based chemotherapy in comparison with the ACT.

The studies KEYNOTE 021G (cohort G of the KEYNOTE 021 study) and KEYNOTE 189 are ongoing randomized, controlled parallel-group studies. The KEYNOTE 021G study is an open-label study that compares pembrolizumab + carboplatin-based chemotherapy with a carboplatin-based chemotherapy. The KEYNOTE 189 study is a blinded study that compares pembrolizumab + platinum-based chemotherapy with platinum-based chemotherapy.

Both studies included adults with histologically or cytologically confirmed stage IV non-squamous NSCLC without EGFR mutation or ALK translocation. A prior systemic therapy against NSCLC stage IIIB or IV was not allowed in either of the two studies.

The KEYNOTE 021G study included a total of 123 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab in combination with carboplatin and pemetrexed (N = 60) or to treatment exclusively with carboplatin and pemetrexed (N = 63). The KEYNOTE 189 study included a total of 616 patients who were randomized in a 2:1 ratio either to treatment with pembrolizumab in combination with carboplatin or cisplatin each with pemetrexed (N = 410) or to treatment exclusively with carboplatin or cisplatin each with pemetrexed (N = 206). Prior to randomization, the investigator decided on whether a patient received cisplatin or carboplatin as platinum component.

In both studies, administration of pembrolizumab concurred with the requirements of the Summary of Product Characteristics (SPC). Administration of the platinum-based chemotherapy was identical in each of the both study arms of the KEYNOTE 021G and KEYNOTE 189 studies and complied with the requirements of the respective SPC or the

Pharmaceutical Directive for off-label use (Appendix VI to Section K) (see below). The platinum component of the platinum-based chemotherapy was administered for a maximum of 4 cycles in both studies. After the initial 4 cycles, administration of pemetrexed was continued at 3-week intervals in the KEYNOTE 189 study; in the KEYNOTE 021G study, this decision was made at the investigator's discretion.

The objective response rate was the primary outcome of the KEYNOTE 021G study; primary outcomes of the KEYNOTE 189 study were "progression-free survival (PFS)" and "overall survival". Further patient-relevant outcomes in the KEYNOTE 021G were "overall survival" and "adverse events (AE)", in the KEYNOTE 189 study it were "symptoms", "health-related quality of life" and "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 profiles of the two substances and on the existing comorbidities.

In the studies KEYNOTE 189 and KEYNOTE 021G, 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 had 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

One subpopulation of each of the two studies KEYNOTE 189 and KEYNOTE 021G is relevant for the present research question 1. These subpopulations comprised patients with metastatic non-squamous NSCLC and a PD-L1 expression < 50%. Moreover, the patients had have to be treated in compliance with the specifications of the Pharmaceutical Directive for off-label use of carboplatin. In its dossier, the company presented corresponding analyses for this subpopulation for the two studies KEYNOTE 021G (N = 40) and KEYNOTE 189 (N = 250). This subpopulation represented the patient population relevant for the present research question and was 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 studies KEYNOTE 021G and KEYNOTE 189 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 for second-line treatment.

At the time point of the data cut-off of 31 May 2017, a total of 7 (35%) patients of the relevant subpopulation had switched from the comparator arm to treatment with pembrolizumab in the KEYNOTE 021G study. In the KEYNOTE 189 study, these were 25 (28.4%) patients of the relevant subpopulation at the time point of the data cut-off of 8 November 2017.

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

When describing the operationalizations of the outcome "overall survival" for the studies KEYNOTE 407 and KEYNOTE 042 in its dossier on squamous NSCLC (Module 4 C), 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 intention to treat (ITT) analyses, the corresponding result tables indicate that the observation was censored at the time point of the data cut-off. These contradictory data also apply to the KEYNOTE 042 study, which the company included in both its dossier on squamous NSCLC (Module 4 C) and its dossier on non-squamous NSCLC (Module 4 B) (see research question 2). In its dossier on non-squamous NSCLC (Module 4 B), the company did not state that patients were censored at the time point of the treatment switch. However, it neither stated that the patients who had switched to monotherapy with pembrolizumab had not been censored. When describing the risk of bias in its dossier on non-squamous NSCLC (Module 4 B), the company moreover stated that it was going to consider the treatment switch of the patients in the analysis methods at outcome level. It remains unclear, however, what it refers to in this context.

The results on overall survival presented by the company are not usable due to these contradictory data in its dossier on pembrolizumab in NSCLC (Module 4 B on non-squamous NSCLC and Module 4 C on squamous NSCLC). Meaningful interpretation requires an 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 two studies KEYNOTE 021G and KEYNOTE 189. The risk of bias is high for the outcomes on symptoms (recorded using the symptom scales of the European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 [QLQ-LC13] and the EORTC Quality of Life Questionnaire Lung Cancer 13 [QLQ-LC13]) and health-related quality of life (recorded using the functional scales of the EORTC QLQ-C30) recorded in the KEYNOTE 189 study. The

results of the outcome “discontinuation due to AEs” were rated as potentially highly biased in the KEYNOTE 021G study. In the KEYNOTE 189 study, 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. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Morbidity

Outcomes of the category “morbidity” were only recorded in the KEYNOTE 189 study.

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

- Constipation

In the KEYNOTE 189 study, a statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy was shown for the outcome “constipation”. However, the extent of the effect in this non-serious/non-severe symptom was no more than marginal. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

- Dyspnoea, fatigue, insomnia, pain, appetite loss, diarrhoea as well as nausea and vomiting

In the KEYNOTE 189 study, no statistically significant difference between the treatment groups was shown for the any of outcomes "dyspnoea", "fatigue", "insomnia", “pain”, "appetite loss", “diarrhoea” as well as "nausea and vomiting". Hence, there was no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for any of these outcomes; an added benefit is therefore not proven.

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

A statistically significant difference between the treatment arms was not shown for any of the outcomes of the EORTC QLQ-LC13 symptom scales (dyspnoea, pain [thorax], pain [arm/shoulder], pain [other], cough, haemoptysis, alopecia, dysphagia, sore mouth and peripheral neuropathy). Hence, there was no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for these outcomes; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There were no evaluable data for the outcome "health status" measured with the Visual Analogue Scale (VAS) of the European Quality of Life Questionnaire 5 Dimensions (EQ-5D) in the KEYNOTE 189 study. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Health-related quality of life

The outcomes of the category “health-related quality of life” were also only recorded in the KEYNOTE 189 study.

EORTC QLQ-C30 (functional scales)

A statistically significant difference between the treatment arms was not shown for any of the outcomes of the EORTC QLQ-C30 functional scales (global health status, emotional functioning, cognitive functioning, physical functioning, role functioning and social functioning). Hence, there was no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for these outcomes; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs), immune-related SAEs

In both studies (KEYNOTE 021G and KEYNOTE 189), there are no usable analyses for the outcomes “SAEs” and “immune-related SAEs”. This resulted in no hint of greater or lesser harm from pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

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

A statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy was shown for the outcome “severe AEs (CTCAE grade ≥ 3)” in the meta-analysis of the KEYNOTE 021G and KEYNOTE 189 studies. This resulted in an indication of lesser harm from pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

Discontinuation due to AEs

The meta-analysis of the studies KEYNOTE 021G and KEYNOTE 189 showed 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 + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

Immune-related AEs and immune-related severe AEs (CTCAE grade ≥ 3)

Usable results for the outcomes "immune-related AEs" and "immune-related severe AEs (CTCAE grade ≥ 3)" are only available from the KEYNOTE 189 study. In each case, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

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 + platinum-based chemotherapy in patients with PD-L1 expression ≥ 50% in comparison with monotherapy with pembrolizumab. Therefore, the company presented an adjusted indirect comparison with the common comparator "platinum-based chemotherapy" for the assessment of the added benefit of pembrolizumab + platinum-based chemotherapy in patients with PD-L1 expression ≥ 50%.

The studies KEYNOTE 021G and KEYNOTE 189 on the comparison of pembrolizumab + platinum-based chemotherapy with a platinum-based chemotherapy were identified for the intervention. The studies KEYNOTE 024 and KEYNOTE 042 on the comparison of pembrolizumab (monotherapy) with platinum-based chemotherapy were identified for the comparator.

Study characteristics

Studies with the intervention: KEYNOTE 021G and KEYNOTE 189

The KEYNOTE 021G and KEYNOTE 189 studies were also used for the assessment of the added benefit of research question 1 (patients with PD-L1 expression < 50%). The description of the study designs can be found in research question 1 of the executive summary.

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

As already described in the dossier assessment on project A17-06, the KEYNOTE 024 study is a randomized, open-label, controlled study. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation, whose tumours had a PD-L1 expression ≥ 50%. Prior systemic antineoplastic treatment for the metastatic stage was not allowed.

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based combination chemotherapy (N = 151). The treatment suitable for each patient was specified by an investigator on an individual basis prior to randomization.

The administration of pembrolizumab concurred with the requirements of the SPC. The platinum-based chemotherapies (cisplatin or carboplatin + pemetrexed) relevant as common comparator for research question 2 were also administered largely in compliance with the respective SPCs or the pharmaceutical directive for off-label use (Appendix VI to Section K) (see below). The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the KEYNOTE 024 study. Thereafter, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended.

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

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 NSCLC with locally advanced or metastatic tumours with PD-L1 expression ≥ 1%. Prior systemic treatment was not allowed. The treatment option (carboplatin + paclitaxel or carboplatin + pemetrexed) suitable for a patient in case of randomization to the comparator arm was specified by an investigator on an individual basis.

Patients in the intervention arm received pembrolizumab in accordance with the SPC. Pemetrexed, which was a component of the platinum-based chemotherapy (carboplatin + pemetrexed) relevant as common comparator for research question 2, was also administered in compliance with the requirements of the SPC. In the KEYNOTE 042 study, patients with non-squamous histology received the platinum component of the chemotherapy for a maximum of 4 to 6 cycles. After at least 4 cycles, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended.

"Overall survival" was the primary outcome of the study. Patient-relevant secondary outcomes were 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 VI to Section K of the Pharmaceutical Directive must be considered for carboplatin treatment in the present therapeutic indication. Neither for the studies KEYNOTE 021G and KEYNOTE 189, nor for the studies KEYNOTE 024 and KEYNOTE 042, 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 had 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 off-label use of carboplatin in the present therapeutic indication.

Subpopulations of the studies relevant for the research question

One subpopulation of each of the included studies was also relevant for research question 2. In the studies KEYNOTE 189 and KEYNOTE 021G as well as KEYNOTE 024 and KEYNOTE 042, these were patients with metastatic non-squamous NSCLC and PD-L1 expression ≥ 50%. Moreover, as with research question 1, the patients with carboplatin as treatment component had have to be treated in compliance with the requirements of the Pharmaceutical Directive for off-label use. A further limitation of the study populations for the KEYNOTE 024 and KEYNOTE 042 studies resulted from the available common comparator consisting of either cisplatin or carboplatin in combination with pemetrexed. In its dossier, the company presented corresponding analyses for these subpopulations for the four studies KEYNOTE 189 and KEYNOTE 021G as well as KEYNOTE 024 and KEYNOTE 042. Overall, 470 patients from the 4 studies (pembrolizumab + platinum-based chemotherapy: 95; pembrolizumab monotherapy: 165; common comparator [platinum-based chemotherapy]: 210) were included in the assessment.

Similarity of the studies in the adjusted indirect comparison

The difference between the studies KEYNOTE 021G and KEYNOTE 189 as well as KEYNOTE 024 and KEYNOTE 042 consists chiefly in the common comparator: In the studies KEYNOTE 189 and KEYNOTE 024, patients of the relevant subpopulation in the comparator arm received either carboplatin or cisplatin in combination with pemetrexed; in the studies KEYNOTE 021G and KEYNOTE 042, all patients of the relevant subpopulation in the comparator arm received only carboplatin with pemetrexed. Another difference consists in the characteristic “region”: In KEYNOTE 042, the proportion of patients from non-EU countries is clearly higher than in the studies KEYNOTE 189 and KEYNOTE 024. Information on KEYNOTE 021G is missing.

The assumption of similarity for the indirect comparison did not have to be discarded due to the described differences between the studies. However, possible 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 all four studies, patients of the comparator arm had switched to monotherapy with pembrolizumab after confirmed disease progression. For patients of research question 2 (PD-L1 expression ≥ 50%), this switch of treatment corresponds to the approved use of pembrolizumab in second-line treatment.

In the relevant subpopulations, these were 4 (40%) patients in the KEYNOTE 021G study, 11 (27.5%) in the KEYNOTE 189 study, 28 (37.5%) in the in the KEYNOTE 024 study and 16 (18.6%) in the KEYNOTE 042 study.

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

When describing the operationalizations of the outcome "overall survival" for the studies KEYNOTE 407 and KEYNOTE 042 in its dossier on squamous NSCLC (Module 4 C), 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 corresponding result tables indicate that the observation was censored at the time point of the data cut-off. These contradictory data also apply to the KEYNOTE 042 study, which the company included both in its dossier on squamous NSCLC (Module 4 C) and its dossier on non-squamous NSCLC (Module 4 B). In its dossier on non-squamous NSCLC (Module 4 B), the company did not state that patients were censored at the time point of the treatment switch. However, it neither stated that the patients who had switched to monotherapy with pembrolizumab had not been censored. When describing the risk of bias in its dossier on non-squamous NSCLC (Module 4 B), the company moreover stated that it was going to consider the treatment switch of the patients in the analysis methods at outcome level. It remains unclear, however, what it refers to in this context.

The results on "overall survival" presented by the company are not usable due to these contradictory data in its dossier on pembrolizumab in NSCLC (Module 4 B on non-squamous NSCLC and Module 4 C on squamous NSCLC). Meaningful interpretation requires an 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 all 4 studies.

The risk of bias is high for the outcomes on symptoms (recorded using the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales) and health-related quality of life (recorded using the functional scales of the EORTC QLQ-C30) recorded in the studies KEYNOTE 189 and KEYNOTE 024. No indication of added benefit can be derived for the outcomes on symptoms and on health-related quality of life, since only results from 1 study with a high bias potential are available for each of these outcomes on each side of the indirect comparison.

The results of the outcome "discontinuation due to AEs" were rated as potentially highly biased in the studies KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042. In the KEYNOTE 189 study, the certainty of conclusions was restricted for this outcome despite a low risk of bias. The risk of bias for the outcomes "severe AEs (CTCAE grade ≥ 3)", "immune-related AEs" and "immune-related severe AEs (CTCAE grade ≥ 3)" was rated as high.

Results

Overall consideration of the available data for the indirect comparison 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. In the indirect comparison, usable analyses were only available for the outcomes "severe AEs

(CTCAE grade ≥ 3)" and "discontinuation due to AEs". 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 021G, KEYNOTE 189, KEYNOTE 024 and KEYNOTE 042 for the indirect comparison. Overall, the data presented by the company for indirect comparison are not suitable for deriving an added benefit of pembrolizumab + platinum-based chemotherapy as first-line treatment of adults with metastatic non-squamous NSCLC without EGFR or ALK-positive mutations with a PD-L1 expression ≥ 50% in comparison with the ACT. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

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

On the basis of the results presented, the extent and probability of the added benefit of the drug pembrolizumab + platinum-based chemotherapy compared with the ACT is assessed as follows:

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

Based on the available analyses, overall assessment showed a positive effect for the outcome "severe AEs (CTCAE grade ≥ 3)", which is not offset by negative effects. However, since no usable analyses on "overall survival" are available for the relevant subpopulation, an overall conclusion on the added benefit cannot be drawn.

In summary, no added benefit of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy in comparison with cisplatin or carboplatin each in combination with pemetrexed was proven for adult patients with metastatic non-squamous NSCLC without EGFR or ALK-positive tumour mutations with a PD-L1 expression of < 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 pemetrexed and platinum-based chemotherapy in comparison with pembrolizumab monotherapy in first-line treatment of adults with metastatic non-squamous NSCLC with a PD-L1 expression ≥ 50%.

[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 presents a summary of the probability and extent of the added benefit of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy.

Table 3: Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see also Appendix VI to Section K of the Pharmaceutical Directive *or* ▪ carboplatin in combination with nab-paclitaxel	Added benefit not proven
First-line treatment of the metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with a PD-L1 expression ≥ 50%[b]	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: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

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

2.2 Research question

The aim of the present report was to assess the added benefit of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy as first-line treatment in comparison with the ACT in adult patients with metastatic non-squamous NSCLC without EGFR or ALK-positive tumour mutations.

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 pemetrexed and platinum-based chemotherapy

Research question	**Subindication**	**ACT[a]**
1	First-line treatment of metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see also Appendix VI to Section K of the Pharmaceutical Directive [3]) *or* ▪ carboplatin in combination with nab-paclitaxel
2	First-line treatment of the metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression ≥ 50%[b]	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: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

The company followed the G-BA's specification of the ACT for both research questions and chose a platinum-based combination chemotherapy consisting of either cisplatin or carboplatin each in combination with pemetrexed from the options presented for research question 1.

In the present assessment, the following terms are used for the drug under assessment and the ACT chosen by the company:

- Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy: pembrolizumab + platinum-based chemotherapy
- Cisplatin or carboplatin in combination with pemetrexed: platinum-based chemotherapy

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

To check the completeness of the study pool:

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

Besides the studies KEYNOTE 189 and KEYNOTE 021G already identified by the company, no additional relevant study was identified from the check.

2.3.1.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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 021G (021G[c])	Yes	Yes	No
KEYNOTE 189 (189[c])	Yes	Yes	No
a: Consisting of either cisplatin or carboplatin in combination with pemetrexed. b: Study sponsored by the company. c: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

The study pool includes the studies KEYNOTE 021G and KEYNOTE 189. The study pool concurred with that of the company.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
021G	RCT, open-label, parallel	**Cohort G1:**[c] Adults (≥ 18 years) with histologically or cytologically confirmed stage IIIB or IV non-squamous NSCLC without EGFR mutation or ALK translocation and with an ECOG PS ≤ 1, without prior systemic therapy[d]	**Cohort G1:**[c] ▪ Pembrolizumab in combination with carboplatin-based chemotherapy (N = 60) ▪ carboplatin-based chemotherapy (n = 63) Relevant subpopulation thereof[e]: ▪ Pembrolizumab in combination with carboplatin-based chemotherapy (n = 20) ▪ carboplatin-based chemotherapy (n = 20)	▪ Screening (KEYNOTE 021): up to 28 days before start of treatment ▪ Treatment (cohort G1): until progression, unacceptable side effects, decision by the investigator or the patient, complete response or after maximally 35 cycles of pembrolizumab[f] ▪ Follow-up (cohort G1)[g]: at most until death	26 centres in 2 countries: Taiwan and USA **Cohort G1:** 12/2014–ongoing First data cut-off: 08/2016 (prespecified: primary analysis) Second data cut-off: 05/2017 (post hoc: on request of the European Medicines Agency [EMA])	Primary: objective response rate Secondary: overall survival, AEs
189	RCT, double-blind, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed stage IV non-squamous NSCLC without EGFR mutation or ALK translocation and with an ECOG PS ≤ 1, without prior systemic therapy[d]	▪ Pembrolizumab in combination with platinum-based chemotherapy[h] (N = 410) ▪ Platinum-based chemotherapy[h] (n = 206) Relevant subpopulation thereof[e]: ▪ Pembrolizumab in combination with platinum-based chemotherapy[h] (n = 162) ▪ Platinum-based chemotherapy[h] (n = 88)	▪ Screening: up to 28 days before start of treatment ▪ Treatment: until progression, unacceptable side effects, decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[f] ▪ Follow-up[g]: at most until death	143 centres in 16 countries: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Spain, United Kingdom, USA 02/2016–ongoing Data cut-off: 11/2017 (prespecified, first interim analysis) Final analysis planned to take place after 416 deaths	Primary: PFS, overall survival Secondary: Morbidity, symptoms, health-related quality of life, AEs

(continued)

Table 6: Characteristics of the studies included – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy [a] (continued)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed
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: The other cohorts of the KEYNOTE 021 study are not relevant for the assessment.
d: Without prior systemic therapy of the stage IIIB or IV NSCLC.
e: The relevant subpopulation comprised patients with PD-L1 expression < 50% who, pursuant to the results of the TPC survey of the company, had been treated in accordance with the criteria of the Pharmaceutical Directive for off-label use (Appendix VI to Section K [3]) of carboplatin.
f: Patients in the pembrolizumab arm (KEYNOTE 021G) or in both arms (KEYNOTE 189) could temporarily discontinue treatment after confirmed complete response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab at the investigator's discretion ("second course phase") after subsequent confirmed progression (if certain conditions regarding previous treatment duration and disease status were met). Based on the study documents it should be assumed that none of the patients (KEYNOTE 189) or only < 5% of the patients in the total study population (Institute's calculation) (KEYNOTE 021G) reached the "second course phase".
g: Outcome-specific information is provided in Table 8.
h: Cisplatin or carboplatin (determined at the investigator's discretion prior to randomization) + pemetrexed.

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; n: relevant subpopulation; N: number of randomized 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; vs.: versus

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

Study	Intervention	Comparison
021G	Pembrolizumab 200 mg IV (infusion administered over 30 minutes) every 3 weeks for a maximum of 35 cycles + carboplatin-based combination chemotherapy for: ▪ carboplatin AUC 5 mg/mL/min IV (administered as 15 to 60-minute infusion), every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² IV (administered as 10-minute infusion) every 3 weeks for at least 4 cycles, followed by continued treatment with pemetrexed every 3 weeks at the investigator's discretion	Carboplatin-based combination chemotherapy: ▪ carboplatin AUC 5 mg/mL/min IV (administered as 15 to 60-minute infusion), every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² IV (administered as 10-minute infusion) every 3 weeks for at least 4 cycles, followed by continued treatment with pemetrexed every 3 weeks at the investigator's discretion
	Dose adjustments in case of toxicities ▪ for carboplatin and pemetrexed in line with the SPC ▪ Not allowed for pembrolizumab (treatment could be interrupted or discontinued) **Pretreatment** ▪ Adjuvant therapy > 1 year before diagnosis of the metastatic disease **Non-permitted pretreatment** ▪ systemic treatment of stage IIIB and IV NSCLC **Non-permitted concomitant treatment** ▪ other systemic chemotherapies or biologic treatments ▪ other chemotherapies or immunotherapies ▪ surgical interventions and radiotherapies for tumour control ▪ live vaccines ▪ Corticosteroids (> 7 days) except for the treatment of AEs or as premedication of a platinum-based combination chemotherapy applied in the study ▪ Phenytoin (during carboplatin)	

(continued)

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

Study	Intervention	Comparison
189	Pembrolizumab 200 mg IV (infusion administered over 30 minutes) every 3 weeks for a maximum of 35 cycles + platinum-based combination chemotherapy: ▪ cisplatin 75 mg/m² IV (approx. 30 minutes following pemetrexed infusion) every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² IV (infusion administered over 10 minutes) every 3 weeks or ▪ carboplatin[b] AUC 5 mg/mL/min IV (infusion administered over 15 to 60 minutes), every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² IV (infusion administered over 10 minutes) every 3 weeks	placebo for pembrolizumab (as infusion administered over 30 minutes) every 3 weeks for a maximum of 35 cycles + platinum-based combination chemotherapy: ▪ cisplatin 75 mg/m² IV (approx. 30 minutes following pemetrexed infusion) every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² IV (infusion administered over 10 minutes) every 3 weeks or ▪ carboplatin[b] AUC 5 mg/mL/min IV (infusion administered over 15 to 60 minutes), every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² IV (infusion administered over 10 minutes) every 3 weeks
	Dose adjustments in case of toxicities: ▪ allowed for cisplatin or carboplatin and pemetrexed in line with the protocol ▪ not allowed for pembrolizumab (treatment could be interrupted or discontinued) **Pretreatment** ▪ patients who had received adjuvant or neoadjuvant therapy before could participate in the study, provided that the treatment had been completed ≥ 12 month prior to diagnosis of the metastatic disease **Non-permitted pretreatment** ▪ systemic treatment of stage IV NSCLC **Non-permitted concomitant treatment** ▪ other systemic chemotherapies or biologic treatments ▪ other chemotherapies or immunotherapies ▪ radiotherapies ▪ live vaccines ▪ corticosteroids (> 7 days) except for the treatment of AEs or as premedication of a platinum-based combination chemotherapy applied in the study ▪ phenytoin (during cisplatin/carboplatin)	

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: The carboplatin dose was not to exceed 750 mg.
AE: adverse event; AUC: area under the curve; IV: intravenous; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

Study KEYNOTE 021G and study KEYNOTE 189

The studies KEYNOTE 021G (cohort G of the KEYNOTE 021 study) and KEYNOTE 189 are ongoing randomized, controlled parallel-group studies with similar study design. The KEYNOTE 021G study is an open-label study that compares pembrolizumab + carboplatin-based chemotherapy with a carboplatin-based chemotherapy. The KEYNOTE 189 study was a

blinded study that compared pembrolizumab + platinum-based chemotherapy with platinum-based chemotherapy.

Both studies included adults with histologically or cytologically confirmed stage IV non-squamous NSCLC without EGFR mutation or ALK translocation and ECOG PS ≤ 1 irrespective of the PD-L1 expression. The inclusion criteria of the KEYNOTE 021G study additionally comprised patients with stage IIIB disease. A prior systemic therapy against NSCLC stage IIIB or IV was not allowed in either of the two studies. In the KEYNOTE 189 study, the PD-L1 expression of the tumour tissue was determined using a Dako immunohistochemistry kit, in KEYNOTE 021G, the PD-L1 expression was also determined by means of immunohistochemistry, however, information on the utilized kit is missing. 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.

The KEYNOTE 021G study included a total of 123 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab in combination with carboplatin and pemetrexed (N = 60) or to treatment exclusively with carboplatin and pemetrexed (N = 63). Randomization was stratified by PD-L1 expression (≥ 1%/< 1%).

The KEYNOTE 189 study included a total of 616 patients who were randomized in a 2:1 ratio either to treatment with pembrolizumab in combination with carboplatin or cisplatin each with pemetrexed (N = 410) or to treatment only with carboplatin or cisplatin each with pemetrexed (N = 206). Prior to randomization, the investigator decided on whether a patient received cisplatin or carboplatin as platinum component. Randomization was stratified by the decision on a platinum component (cisplatin/carboplatin), the PD-L1 expression (≥ 1%/< 1%) and the smoking status (never/former and active).

In both studies, administration of pembrolizumab concurred with the requirements of the SPC [4]. The maximum treatment duration for pembrolizumab was 35 cycles in both studies. In both studies (KEYNOTE 021G and KEYNOTE 189), this maximum treatment duration was only reached by approx. < 5% of the patients in the total study population. Administration of the platinum-based chemotherapy was identical in the two study arms of the KEYNOTE 021G and KEYNOTE 189 studies and complied with the requirements of the respective SPC [5,6] or the Pharmaceutical Directive for off-label use (Appendix VI to Section K [3]) (see below). The platinum component of the platinum-based chemotherapy was administered for a maximum of 4 cycles in both studies. After the initial 4 cycles, administration of pemetrexed was continued at 3-week intervals in the KEYNOTE 189 study; in the KEYNOTE 021G study, this decision was made at the investigator's discretion. A total of 92 (76.0%) patients in the total study population of the KEYNOTE 021G study received ≥ 5 cycles of pemetrexed (intervention arm: N = 50 [84.8%]; comparator arm: N = 42 [67.7%]). In the study KEYNOTE 189, 445 (73.3%) patients in the total study population received ≥ 5 cycles of pemetrexed (intervention arm: N = 310 [76.5%]; comparator arm: N = 135 [66.8%]).

In both studies, patients were treated until disease progression, occurrence of unacceptable side effects, or treatment discontinuation due to decision by the investigator or the patient. After disease progression, suitable patients in the comparator arms of both studies could switch to monotherapy with pembrolizumab. There was no other limitation regarding subsequent therapy. At the time point of the data cut-off of 8 November 2017, the proportion of patients with antineoplastic subsequent therapy administered outside of the study protocol in the entire study population of the KEYNOTE 189 study was 30.5 % (N = 125) in the intervention arm and 20.9 % (N = 43) in the comparator arm (see Table 39 of the full dossier assessment). 67 (32.5 %) patients had switched from the comparator arm to treatment with pembrolizumab as monotherapy in accordance with the protocol. At the time point of the data cut-off of 31 May 2017, the proportion of patients receiving antineoplastic subsequent therapy other than pembrolizumab (monotherapy) in the entire study population of the KEYNOTE 021G study was 47.5% (N = 28) in the intervention arm and 45.9% (N = 17) in the comparator arm (see Table 38 of the full dossier assessment). At this time point, 25 (39.7%) patients of the total study population had switched from the comparator arm to pembrolizumab as monotherapy in accordance with the protocol. There was no information on the subsequent therapies for the relevant subpopulation of the two studies.

The objective response rate was the primary outcome of the KEYNOTE 021G study; primary outcomes of the KEYNOTE 189 study were “PFS” and “overall survival”. Further patient-relevant outcomes in the KEYNOTE 021G study were “overall survival” and “AEs”, in the KEYNOTE 189 study it were “symptoms”, “health-related quality of life” and “AEs”.

Implementation of the Pharmaceutical Directive on the use of carboplatin

In the first-line treatment, carboplatin is only approved for the treatment of NSCLC in combination with nab-paclitaxel [7], 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 can be prescribed for patients with advanced NSCLC in the off-label use. Thereby, application in accordance with the 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 [3].

In the studies KEYNOTE 189 and KEYNOTE 021G, 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). Before randomization, the investigator allocated the patients to the platinum components cisplatin or carboplatin on an individual basis in the study KEYNOTE 189. For KEYNOTE 021G, carboplatin was the only treatment option. The company presented the results on the survey of investigators on the reasons for treatment with carboplatin in the dossier.

Based on these results, the company restricted the implementation of the ACT to patients who fulfilled the requirements of the TPC survey, i.e. patients

- whom the investigator deemed suitable for cisplatin-based treatment and who were therefore to receive cisplatin-based treatment
- or whom the investigator deemed unsuitable for cisplatin-based treatment and who therefore received treatment with carboplatin
- or 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 safety 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 on 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.

Relevant subpopulations for research question 1 (PD-L1 expression < 50 %)

One subpopulation of each of the two studies KEYNOTE 189 and KEYNOTE 021G is relevant for the present research question 1. These subpopulations comprised patients with metastatic non-squamous NSCLC and a PD-L1 expression < 50%. Moreover, the patients had have to be treated in compliance with the specifications of the Pharmaceutical Directive for off-label use of carboplatin. In its dossier, the company presented corresponding analyses for this subpopulation for the two studies KEYNOTE 021G (N = 40) and KEYNOTE 189 (N = 250). This subpopulation represented the patient population relevant for the present research question and was used for the benefit assessment.

Data cut-offs

Those data cut-offs for which the company had processed the data in Module 4 B were used. For the KEYNOTE 021G study, this was the hitherto last data cut-off of 31 May 2017, which had been conducted post hoc at the request of the European Medicines Agency (EMA). From the KEYNOTE 189 study, the hitherto only data cut-off of 8 November 2017 was used. This was an interim analysis planned a priori after approx. 373 PFS events.

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

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
021G	
Mortality	
Overall survival	▪ After end of treatment: every 3 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 dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first)
189	
Mortality	
Overall survival	▪ After the end of treatment (except due to progression): every 6 weeks until progression ▪ After progression or initiation of a new antineoplastic 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 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 was initiated, whichever occurred first)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed

AE: adverse event; EORTC: European Organization 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; VAS: visual analogue scale; vs.: versus

In both studies (KEYNOTE 021G and KEYNOTE 189), the observation periods for the outcomes “morbidity” and “health-related quality of life” (as far as recorded) as well as “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”.

Characteristics of the study population

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

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

Study	**021G**		**189**	
Data cut-off				
Characteristics	**Pembrolizumab + carboplatin-based chemotherapy**	**Carboplatin-based chemotherapy**	**Pembrolizumab + platinum-based chemotherapy[a]**	**Platinum-based chemotherapy[a]**
Category				
	N[b] = 20	**N[b] = 20**	**N[b] = 162**	**N[b] = 88**
Age [years], mean (SD)	63 (10)	62 (12)	62 (10)	62 (9)
Sex [F/M], %	45/55	70/30	36/64	44/56
Ethnicity, n (%)				
White	15 (75.0)	18 (90.0)	150 (92.6)	81 (92.0)
Non-white	5 (25.0)	2 (10.0)	11 (6.8)	7 (8.0)
Unknown	0 (0)	0 (0)	1 (0.6)	0 (0)
Region, n (%)				
EU	ND	ND	105 (64.8)	61 (69.3)
Non-EU	ND	ND	57 (35.2)	27 (30.7)
Smoking status, n (%)				
Never-smoker	5 (25.0)	2 (10.0)	21 (13.0)	14 (15.9)
Former	11 (55.0)	14 (70.0)	108 (66.7)	54 (61.4)
Active	4 (20.0)	4 (20.0)	33 (20.4)	20 (22.7)
ECOG PS, n (%)				
0	8 (40.0)	12 (60.0)	78 (48.1)	42 (47.7)
1	11 (55.0)	8 (40.0)	84 (51.9)	46 (52.3)
2	1 (5.0)	0 (0)	0 (0)	0 (0)
Disease stage, n (%)				
IIIB	0 (0)	0 (0)	3 (1.9)	1 (1.1)
IV	20 (100.0)	20 (100.0)	159 (98.1)	87 (98.9)
Metastases, n (%)				
M0	0 (0)	1 (5.0)	2 (1.2)	1 (1.1)
M1	5 (25.0)	4 (20.0)	2 (1.2)	0 (0)
M1A	6 (30.0)	4 (20.0)	57 (35.2)	28 (31.8)
M1B	9 (45.0)	9 (45.0)	101 (62.3)	59 (67.0)
MX	0 (0)	2 (10.0)	0 (0)	0 (0)
Time since initial diagnosis [months]				
mean (SD)	10.3 (18.3)	13.6 (32.6)	6.3 (12.4)	6.8 (13.2)
median [min; max]	2.1 [0.9; 64.6]	2.0 [0.9; 144.6]	1.7 [0.2; 64.9]	1.5 [0.5; 62.8]

(continued)

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

Study	**021G**		**189**	
Data cut-off				
Characteristics	**Pembrolizumab + carboplatin-based chemotherapy**	**Carboplatin-based chemotherapy**	**Pembrolizumab + platinum-based chemotherapy[a]**	**Platinum-based chemotherapy[a]**
Category				
	N[b] = 20	**N[b] = 20**	**N[b] = 162**	**N[b] = 88**
Tumour size at start of the study [mm]				
mean (SD)	61.6 (45.5)	83.5 (52.0)	97.6 (72.6)	105.3 (55.9)
median [min; max]	45.0 [13.0; 185.0]	62.0 [17.0; 179.0]	75.5 [13.0; 419.7]	90.7 [21.1; 256.1]
Brain metastases, n (%)				
yes	5 (25.0)	1 (5.0)	20 (12.3)	12 (13.6)
no	15 (75.0)	19 (95.0)	142 (87.7)	76 (86.4)
Histology, n (%)				
adenocarcinoma	19 (95.0)	15 (75.0)	154 (95.1)	86 (97.7)
not further specified	1 (5.0)	4 (20.0)	5 (3.1)	1 (1.1)
other	0 (0)	1 (5.0)	3 (1.9)	1 (1.1)
Prior therapies, n (%)				
adjuvant/neo-adjuvant prior therapy	3 (15.0)	0 (0)	6 (3.7)	8 (9.1)
Platinum-based chemotherapy, n (%)				
cisplatin	–	–	75 (46.3)	41 (46.6)
carboplatin	10 (100)	10 (100)	87 (53.7)	47 (53.4)
Treatment discontinuation, n (%)	ND[c]	ND[c]	ND[c]	ND[c]
Study discontinuation, n (%)	ND[c]	ND[c]	ND[c]	ND[c]

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed
b: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: There was no information on treatment and study discontinuations for the relevant subpopulation.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: number of patients in the category; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients in the relevant subpopulation; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Overall, the characteristics of the relevant subpopulations are sufficiently comparable both between the studies and between the two treatment arms in the individual studies. The mean age of the included patients in the relevant subpopulations of the studies KEYNOTE 021G and KEYNOTE 189 was 62 years; almost the majority of them were male and clearly most of them were white. Almost all patients had stage IV disease and most of them had no brain metastases. The median time since the initial diagnosis was approximately 1.5 to 2 months.

The major difference between the studies is ascribed to the different treatment options within the framework of the platinum-based chemotherapy already described in Section 2.3.1.2.While the patients in the KEYNOTE 189 study received both carboplatin and cisplatin as platinum component of the chemotherapy, all patients in KEYNOTE 021G received carboplatin.

Treatment switch from the treatment arm with exclusively platinum-based chemotherapy to monotherapy with pembrolizumab after disease progression

As described in Section 2.3.1.2, suitable patients in the two studies KEYNOTE 021G and KEYNOTE 189 could switch from the control arm to monotherapy with pembrolizumab after disease progression. This treatment is an approved therapy in the present line of treatment for patients with PD-L1 expression ≥ 1% [8]. In the relevant subpopulations of the KEYNOTE 021G and KEYNOTE 189 studies, not all patients in the control arm had PD-L1 expression ≥ 1% (patients with PD-L1 expression ≥ 1%: KEYNOTE 021G: 30%; KEYNOTE 189: 48%).

At the time point of the data cut-off of 31 May 2017, a total of 7 (35%) patients of the relevant subpopulation had switched from the comparator arm to treatment with pembrolizumab in the KEYNOTE 021G study. In the KEYNOTE 189 study, these were 25 (28.4%) patients of the relevant subpopulation at the time point of the data cut-off of 8 November 2017. In both studies, also patients with PD-L1 expression < 1% in the relevant subpopulations switched from the control arm to monotherapy with pembrolizumab and thus to an unapproved subsequent therapy.

The company presented Kaplan-Meier curves for the time to treatment switch (see Figure 2 and Figure 3). The figures show that the majority of these treatment switches took place between 3 and 12 months (KEYNOTE 189) or between 0 and 6 months (KEYNOTE 021G). In both studies, large proportions of patients had thus switched from the control arm to monotherapy with pembrolizumab at early time points.

Methods used for the analysis 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 data of the company in its dossier on pembrolizumab in NSCLC (Module 4 B on non-squamous NSCLC and Module 4 C on squamous NSCLC). This is explained below.

When describing the operationalizations of the outcome “overall survival” for the studies KEYNOTE 407 and KEYNOTE 042 in its dossier on squamous NSCLC (Module 4 C), 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 corresponding result tables indicate that the observation was censored at the time point of the data cut-off. These contradictory data also apply to the KEYNOTE 042 study, which the company included in both its dossier on squamous NSCLC (Module 4 C) and its dossier on non-squamous NSCLC (Module 4 B) (see research question 2). In its dossier on non-squamous NSCLC (Module 4 B), the company did

not state that patients were censored at the time point of the treatment switch. However, it neither stated that the patients who had switched to monotherapy with pembrolizumab had not been censored. When describing the risk of bias in its dossier on non-squamous NSCLC (Module 4 B), the company moreover stated that it was going to consider the treatment switch of the patients in the analysis methods at outcome level. It remains unclear, however, what it refers to in this context.

In the study documents of the KEYNOTE 021G and the KEYNOTE 189 studies, "overall survival" was operationalized as period between randomization and death for any reason. The analyses on "overall survival" planned primarily in the studies are ITT analyses. As in the dossier on squamous NSCLC (module 4 C), the results tables of the dossier on non-squamous NSCLC (module 4 B) indicate in connection with the ITT analyses that the observation was censored at the time of the data cut-off.

Overall, 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% vs. ≥ 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 + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + platinum-based chemotherapy[a]**	**Platinum-based chemotherapy[a]**
021G	N = 19	N = 19
Treatment duration [months]		
Median [min; max]	10.1 [0.7; 22.6]	3.4 [0.0; 25.0]
Mean (SD)	10.5 (6.4)	6.2 (7.4)
Observation period [months]		
Overall survival		
Median [min; max]	20.1 [1.1; 29.0]	13.3 [0.3; 26.5]
Mean (SD)	17.2 (7.9)	13.4 (9.2)
Morbidity	Not recorded	
Health-related quality of life	Not recorded	
Side effects (SAEs)	No usable data	
189	N = 161	N = 87
Treatment duration [months]		
Median [min; max]	6.1 [0.0; 19.6]	4.2 [0.0; 17.3]
Mean (SD)	6.9 (4.6)	5.5 (4.4)
Observation period [months]		
Overall survival		
Median [min; max]	10.1 [0.6; 19.6]	9.8 [0.7; 19.8]
Mean (SD)	10.4 (4.3)	9.6 (4.7)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (SAEs)	No usable data	

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.

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

In the KEYNOTE 021G study, the duration of treatment in the intervention arm was approx. 10 months and thus almost 3 times longer than in the comparison arm (approx. 3 months). The observation period for “overall survival” was also clearly longer in the intervention arm than in the comparator arm.

In KEYNOTE 189, treatment duration in the intervention arm was approx. 6 months and thus also clearly longer than in the comparator arm, where it was approx. 4 months. However, in this study, the observation duration for “overall survival” was approx. 10 months in boths arms and thus almost equal. 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 the category “side effects”; or the data were not usable.

In its dossier, the company provided data on the observation period of SAEs in the studies KEYNOTE 021G and KEYNOTE 189. However, these data are not usable 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 studies KEYNOTE 021G and KEYNOTE 189 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 in the comparator arm who had switch treatment 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 2.3.2.2).

Moreover, the company presented no data on the reasons for the treatment discontinuation for the relevant subpopulation for both studies.

For those outcomes for which data on observation periods are missing, it is assumed that there is a similarly large difference in observation periods between the treatment arms as in the treatment duration of the respective study, as their follow-up was limited (see Table 8 for planned follow-up).

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 + platinum-based chemotherapy[a] vs. platinum-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			
021G	Yes	Yes	No	No	Yes	Yes	Low
189	Yes	Yes	Yes	Yes	Yes	Yes	Low

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
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.

Limitations resulting for the KEYNOTE 021G study from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

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
  - Overall survival
- Morbidity
  - Symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC 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
  - Discontinuation due to AEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Immune-related AEs, SAEs and severe AEs (CTCAE grade ≥ 3)
  - If applicable, further specific AEs

The choice of patient-relevant outcomes concurred with that of the company. However, in its dossier, the company presented further outcomes as supplementary information (see Section 2.6.4.3 of the full dossier assessment).

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

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

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
021G	No[b]	No[c]	No[c]	No[c]	No[b]	Yes	Yes	No[b]	No[b]	No[b]	No[b]
189	No[b]	Yes	No[b]	Yes	No[b]	Yes	Yes	Yes	No[b]	Yes	No[b]

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: No usable analyses available for the relevant subpopulation; for reasons, see Sections 2.3.1.2 as well as Sections 2.6.4.2 and 2.6.4.3.2 of the full dossier assessment.
c: Outcome not recorded.

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; 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

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 + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Study	Study level	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
021G	L	–[b]	–[c]	–[c]	–[c]	–[b]	H[d]	H[e]	–[b]	–[b]	–[b]	–[b]
189	L	–[b]	H[f]	–[b]	H[f]	–[b]	L[g]	H[e]	H[e]	–[b]	H[e]	–[b]

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: No usable analyses available for the relevant subpopulation; for reasons, see Section 2.3.1.2 as well as Sections 2.6.4.2 and 2.6.4.3.2 of the full dossier assessment.
c: Outcome not recorded.
d: Lack of blinding in subjective recording of outcomes.
e: Missing data on the observation period for the intervention arm and the control arm.
f: Large proportion of patients (> 10 percentage points) in the relevant subpopulation who were not considered in the analysis; decreasing response to questionnaires in the relevant subpopulation over the course of the study.
g: 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).
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; QLQ-C30: Quality of Life Questionnaire - Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Usable analyses on the outcomes "overall survival", "SAEs", "immune-related SAEs" and on further specific AEs are missing for both studies (see Section 2.3.1.2 as well as Sections 2.6.4.2 and 2.6.4.3.2 of the full dossier assessment). This also applies to the immune-related AEs and immune-related severe AEs (CTCAE grade ≥ 3) in the KEYNOTE 021G study. "Health status" was not recorded in the KEYNOTE 021G study, for study KEYNOTE 189, there are no usable analyses on "health status" (see Section 2.6.4.3.2 of the full dossier assessment). Therefore, the risk of bias of the results was not assessed for these outcomes. There is a high risk of bias for all other outcomes of both studies (KEYNOTE 021G and KEYNOTE 189), except for the outcome "discontinuation due to AEs" in KEYNOTE 189. This is justified below by outcome category.

The risk of bias for the results on the outcomes on symptoms and health-related quality of life, which were only recorded in the KEYNOTE 189 study, is rated as high due to the large proportions of patients who had not been considered in the analyses. On the other hand, the number of returned questionnaires decreased in the course of the studies.

The results of the outcome "discontinuation due to AEs" were rated as potentially highly biased in the KEYNOTE 021G study due to the open-label study design. In the KEYNOTE 189 study, the certainty of conclusions for the results on the outcome "discontinuation due to AEs" is restricted despite a low risk of bias (see Section 2.6.4.2 of the full dossier assessment).

Due to the lacking data on the observation period, the risk of bias for the results on the outcomes "severe AEs (CTCAE grade ≥ 3)", (KEYNOTE 021G and KEYNOTE 189), "immune-related AEs" (only KEYNOTE 189) and "immune-related severe AEs (CTCAE grade ≥ 3)" (only KEYNOTE 189) was rated as high. It could not be assessed whether a relevant number of incomplete observations due to potentially informative reasons was existent (see Section 2.6.4.2 of the full dossier assessment).

The company rated the risk of bias for the results of all outcomes as low.

2.3.2.3 Results

Table 14 summarizes the results on the comparison of pembrolizumab + platinum-based chemotherapy in patients with metastatic non-squamous NSCLC and PD-L1 expression < 50% with solely platinum-based chemotherapy. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The company did not present the Kaplan-Meier curves on the included outcomes with usable analyses for the relevant subpopulation on which the meta-analyses are based. For the outcomes on symptoms, which were only recorded in the KEYNOTE 189 study, the company only presented Kaplan-Meier curves if a statistically significant difference between the treatment groups was shown.

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 subpopulations on all AEs, severe AEs (CTCAE degree ≥ 3), discontinuation due to AEs and immune-related AEs. On the Preferred Term (PT) level according to MedDRA, results on event time analyses for the relevant subpopulations are neither available for the individual studies nor for the meta-analysis. For PTs, event rates are only presented if the corresponding SOC shows a statistically significant difference between the treatment arms in the respective 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 (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Outcome category Outcome Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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[b]
Mortality					
Overall survival	No usable analyses				
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales)[c]					
Dyspnoea					
021G			Outcome not recorded		
189	161	7.4 [3.5; 19.5] 62 (38.5)	86	5.1 [2.8; 9.0] 38 (44.2)	0.88 [0.58; 1.35]; 0.564
Fatigue					
021G			Outcome not recorded		
189	161	1.4 [1.1; 2.1] 88 (54.7)	86	1.4 [0.8; 1.6] 57 (66.3)	0.73 [0.52; 1.03]; 0.071
Insomnia					
021G			Outcome not recorded		
189	161	NA [8.0; NC] 49 (30.4)	86	4.1 [2.6; NC] 34 (39.5)	0.71 [0.45; 1.12]; 0.140
Pain					
021G			Outcome not recorded		
189	161	5.3 [2.5; 8.3] 71 (44.1)	86	2.6 [1.5; 5.3] 43 (50.0)	0.77 [0.52; 1.14]; 0.195
Appetite loss					
021G			Outcome not recorded		
189	161	7.2 [4.9; NC] 60 (37.3)	86	6.9 [2.8; NC] 33 (38.4)	1.02 [0.66; 1.58]; 0.917
Diarrhoea					
021G			Outcome not recorded		
189	161	NA [5.2; NC] 49 (30.4)	86	11.3 [4.8; NC] 28 (32.6)	0.92 [0.57; 1.48]; 0.718

(continued)

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

Outcome category Outcome Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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[b]
Nausea and vomiting					
021G				Outcome not recorded	
189	161	2.1 [1.4; 4.9] 79 (49.1)	86	1.6 [1.4; 5.3] 46 (53.5)	0.94 [0.65; 1.37]; 0.748
Constipation					
021G				Outcome not recorded	
189	161	9.7 [8.0; NC] 54 (33.5)	86	2.5 [1.6; 9.0] 42 (48.8)	0.59 [0.38; 0.90]; 0.013
Symptoms (EORTC QLQ-LC13 symptom scales)[c]					
Dyspnoea					
021G				Outcome not recorded	
189	161	2.1 [1.4; 2.9] 92 (57.1)	86	2.6 [1.7; 3.7] 47 (54.7)	1.13 [0.78; 1.61]; 0.521
Pain (thorax)					
021G				Outcome not recorded	
189	161	12.1 [8.0; 19.5] 46 (28.6)	86	11.8 [7.4; NC] 21 (24.4)	1.11 [0.65; 1.91]; 0.694
Pain (arm/shoulder)					
021G				Outcome not recorded	
189	161	NA [11.1; NC] 40 (24.8)	86	NA [3.6; NC] 25 (29.1)	0.75 [0.45; 1.25]; 0.265
Pain (other)					
021G				Outcome not recorded	
189	161	7.6 [4.3; NC] 60 (37.3)	86	3.0 [2.6; 8.6] 38 (44.2)	0.71 [0.46; 1.09]; 0.116
Cough					
021G				Outcome not recorded	
189	161	15.2 [5.4; 15.6] 53 (32.9)	86	11.5 [4.1; NC] 27 (31.4)	1.04 [0.65; 1.67]; 0.863

(continued)

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

Outcome category Outcome Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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[b]
Haemoptysis					
021G				Outcome not recorded	
189	161	NA 7 (4.3)	86	NA 7 (8.1)	0.45 [0.16; 1.31]; 0.144
Alopecia					
021G				Outcome not recorded	
189	161	3.1 [2.1; NC] 67 (41.6)	86	11.3 [4.8; NC] 29 (33.7)	1.33 [0.85; 2.10]; 0.215
Dysphagia					
021G				Outcome not recorded	
189	161	NA [11.5; NC] 31 (19.3)	86	11.8 [7.4; NC] 21 (24.4)	0.72 [0.41; 1.26]; 0.249
Sore mouth					
021G				Outcome not recorded	
189	161	7.4 [3.1; NC] 60 (37.3)	86	NA [3.0; NC] 26 (30.2)	1.21 [0.75; 1.94]; 0.442
Neuropathy peripheral					
021G				Outcome not recorded	
189	161	6.0 [3.2; 9.0] 65 (40.4)	86	5.1 [2.9; 11.5] 34 (39.5)	0.84 [0.55; 1.29]; 0.430
Health status (EQ-5D VAS)				No usable analyses	
Health-related quality of life					
EORTC QLQ-C30 functional scales[d]					
global health status					
021G				Outcome not recorded	
189	161	5.2 [2.3; 9.7] 70 (43.5)	86	4.1 [2.5; 7.0] 40 (46.5)	1.02 [0.68; 1.52]; 0.939

(continued)

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

Outcome category Outcome Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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[b]
Emotional functioning					
021G				Outcome not recorded	
189	161	17.7 [8.0; 17.7] 49 (30.4)	86	12.5 [3.6; NC] 30 (34.9)	0.87 [0.55; 1.38]; 0.555
Cognitive functioning					
021G				Outcome not recorded	
189	161	5.5 [2.5; 7.4] 73 (45.3)	86	3.6 [2.2; 7.2] 39 (45.3)	0.95 [0.64; 1.42]; 0.809
Physical functioning					
021G				Outcome not recorded	
189	161	5.2 [2.7; 7.8] 75 (46.6)	86	2.9 [2.1; 4.9] 45 (52.3)	0.84 [0.57; 1.23]; 0.369
Role functioning					
021G				Outcome not recorded	
189	161	3.1 [1.7; 7.8] 74 (46.0)	86	2.7 [1.9; 5.0] 43 (50.0)	0.90 [0.62; 1.33]; 0.605
Social functioning					
021G				Outcome not recorded	
189	161	2.1 [1.6; 4.8] 87 (54.0)	86	1.9 [1.4; 3.4] 47 (54.7)	0.90 [0.63; 1.30]; 0.579
Side effects					
AEs (supplementary information)					
021G	19	0.1 [0.1; 0.3] 19 (100.0)	19	0.1 [0.1; 0.3] 18 (94.7)	–
189	161	0.1 [0.1; 0.1] 161 (100.0)	87	0.1 [0.1; 0.1] 85 (97.7)	–

(continued)

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

Outcome category Outcome Study	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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[b]
SAEs	No usable analyses				
Severe AEs (CTCAE grade ≥ 3)					
021G	19	8.2 [2.8; 17.1] 12 (63.2)	19	3.0 [0.7; NC] 10 (52.6)	0.68 [0.28; 1.65]; 0.398[e]
189	161	3.9 [2.8; 5.7] 96 (59.6)	87	3.4 [2.1; 4.1] 64 (73.6)	0.75 [0.54; 1.02]; 0.071[e]
Total					0.74 [0.55; 0.9957]; 0.047[f]
Discontinuation due to AEs					
021G	19	NA [11.8; NC] 3 (15.8)	19	NA [3.7; NC] 4 (21.1)	0.48 [0.10; 2.16]; 0.336[e]
189	161	16.3 [16.0; 17.9] 38 (23.6)	87	18.3 [NC] 13 (14.9)	1.21 [0.64; 2.28]; 0.561[e]
Total					1.05 [0.59; 1.87]; 0.859[f]
Immune-related AEs					
021G	No usable analyses				
189	161	NA 28 (17.4)	87	16.6 [NC] 9 (10.3)	1.46 [0.69; 3.11]; 0.320[e]
Immune-related SAEs	No usable analyses				
Immune-related severe AEs (CTCAE grade ≥ 3)					
021G	No usable analyses				
189	161	NA 12 (7.5)	87	NA 3 (3.4)	1.82 [0.51; 6.46]; 0.354[e]
Further specific AEs	No usable analyses				

(continued)

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

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: HR and CI: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 status, platinum-based chemotherapy and smoking status; two-sided p-value (Wald test).
c: Time to first deterioration; defined as an increase of the score by ≥ 10 points compared with baseline.
d: Time to first deterioration; defined as decrease of the score by ≥ 10 points compared with baseline.
e: HR and CI: Cox proportional hazards model with treatment as covariate; 2-sided p-value (Wald test).
f: HR and CI: on the basis of a common data pool of the studies KEYNOTE 021G and KEYNOTE 189 Cox proportional hazards model with treatment, PD-L1 status, platinum-based chemotherapy and smoking status as covariates, additionally stratified by study; 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: questionnaire on health-related quality of life (Euro QoL-5 dimensions); HR: hazard ratio; N: number of analyzed patients; n: number of patients with (at least) one event; 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; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

On the basis of the available data, at most indications can be determined for all outcomes that were recorded in both KEYNOTE 021G and KEYNOTE 189, and at most hints, e.g. of an added benefit, can be stated for outcomes for which usable data are available from only one of the two studies.

Mortality

Overall survival

There were no usable analyses for this outcome (see Section 2.3.1.2). This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived proof of an added benefit for the outcome “overall survival”.

Morbidity

Outcomes of the category “morbidity” were only recorded in the KEYNOTE 189 study.

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

Constipation

In the KEYNOTE 189 study, a statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy was shown for the outcome “constipation”. The extent of the effect in this non-serious/non-severe symptom was no more than marginal, however. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Dyspnoea, fatigue, insomnia, pain, appetite loss, diarrhoea as well as nausea and vomiting

In the KEYNOTE 189 study, no statistically significant difference between the treatment groups was shown for the any of outcomes "dyspnoea", "fatigue", "insomnia", “pain”, "appetite loss", “diarrhoea” as well as "nausea and vomiting". Hence, there was no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for these outcomes; an added benefit is therefore not proven.

This deviates from the company’s approach, which derived proof of an added benefit for the total outcome category “morbidity”.

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

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

In the KEYNOTE 189 study, 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, dysphagia, sore mouth as well as peripheral neuropathy. Hence, there was no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for these outcomes; an added benefit is therefore not proven.

This deviates from the company’s approach, which derived proof of an added benefit for the total outcome category “morbidity”.

Health status (EQ-5D VAS)

There were no evaluable analyses for the outcome "health status" measured with the EQ-5D VAS in the KEYNOTE 189 study (see Section 2.6.4.3.2 of the full dossier assessment). This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

This deviates from the company’s approach, which derived proof of an added benefit for the total outcome category “morbidity”.

Health-related quality of life

The outcomes of the category “health-related quality of life” were also only recorded in the KEYNOTE 189 study.

EORTC QLQ-C30 (functional scales)

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

In the KEYNOTE 189 study, there was no statistically significant difference between the treatment groups for any of the following outcomes: global health status, emotional functioning, cognitive functioning, physical functioning, role functioning and social functioning. Hence,

there was no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

SAEs

Usable analyses on the outcome "SAEs" are missing for both studies (KEYNOTE 021G and KEYNOTE 189) (see Section 2.3.1.2 and Section 2.6.4.2 of the full dossier assessment). This resulted in no hint of greater or lesser harm from pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

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

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy was shown for the outcome "severe AEs (CTCAE grade ≥ 3)" in the meta-analysis of the KEYNOTE 021G and KEYNOTE 189 studies. This resulted in an indication of lesser harm from pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

Assessment of the effect for this outcome concurs with that of the company, which, however, derived proof of an added benefit for the entire outcome category "side effects".

Discontinuation due to AEs

The meta-analysis of the studies KEYNOTE 021G and KEYNOTE 189 showed 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 + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

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

Immune-related SAEs

Usable analyses on the outcome "immune-related SAEs", are missing for both studies (KEYNOTE 021G und KEYNOTE 189) (see Section 2.3.1.2 as well as Section 2.6.4.2 of the full dossier assessment). This resulted in no hint of greater or lesser harm from pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

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

Immune-related AEs and immune-related severe AEs (CTCAE grade ≥ 3)

Usable results for the outcomes "immune-related AEs" and "immune-related severe AEs (CTCAE grade ≥ 3)" are only available from the KEYNOTE 189 study. In each case, there was no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from pembrolizumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the company's assessment, which derived proof of an added benefit for the entire 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)
- ethnicity (white, non-white)
- smoking status (never, former and active)
- brain metastases (yes, no)
- PD-L1 expression (TPS < 1%, TPS ≥ 1%)
- Platinum component of the chemotherapy (cisplatin, carboplatin)

For the characteristic "ethnicity", subgroup analyses of the relevant subpopulation are only available for the outcome "overall survival", although subgroup analyses for this characteristic had been planned a priori for all outcomes in both studies (KEYNOTE 021G and KEYNOTE 189). Apart from that subgroup analyses of the relevant subpopulation are available for the meta-analysis of the KEYNOTE 021G and KEYNOTE 189 studies for all included patient-relevant outcomes except for the further specific AEs.

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) are 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 + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

Table 15: Subgroups (morbidity, side effects) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Outcome category Outcome Characteristic Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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][b]	p-value[c]
Morbidity						
Symptoms (EORTC QLQ-C30 symptom scales)[d]						
Dyspnoea						
Age						
021G	Outcome not recorded					
189						
< 65 years	85	5.78 [2.23; 19.52] 34 (40.0)	54	7.00 [3.58; 11.47] 20 (37.0)	1.60 [0.86; 2.96]	0.138
≥ 65 years	76	7.43 [5.36; 15.57] 28 (36.8)	32	2.53 [1.41; 7.00] 18 (56.3)	0.45 [0.23; 0.88]	0.019
Total					Interaction:	0.006[e]
Fatigue						
Smoking status						
021G	Outcome not recorded					
189						
Never	21	2.00 [1.41; 8.21] 12 (57.1)	14	0.76 [0.69; 0.89] 12 (85.7)	0.27 [0.10; 0.72]	0.009
Former/active	140	1.41 [0.76; 2.14] 76 (54.3)	72	1.48 [1.15; 2.37] 45 (62.5)	0.87 [0.60; 1.27]	0.476
Total					Interaction:	0.029[e]
Insomnia						
PD-L1 expression						
021G	Outcome not recorded					
189						
TPS < 1%	79	5.09 [2.10; NC] 30 (38.0)	45	5.32 [2.56; NC] 15 (33.3)	1.13 [0.60; 2.15]	0.707
TPS ≥ 1%	82	NA 19 (23.2)	41	3.71 [1.68; NC] 19 (46.3)	0.38 [0.19; 0.75]	0.005
Total					Interaction:	0.022[e]

(continued)

Table 15: Subgroups (morbidity, side effects) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (continued)

Outcome category Outcome Characteristic Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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][b]	p-value[c]
Symptoms (EORTC QLQ-LC13 symptom scales)[d]						
Pain (arm/shoulder)						
Smoking status						
021G	Outcome not recorded					
189						
Never	21	NA [8.21; NC] 5 (23.8)	14	2.53 [0.72; 7.62] 7 (50.0)	0.12 [0.02; 0.61]	0.011
Former/active	140	NA [11.07; NC] 35 (25.0)	72	NA [5.09; NC] 18 (25.0)	0.96 [0.54; 1.70]	0.887
Total					Interaction:	0.018[e]
PD-L1 expression						
021G	Outcome not recorded					
189						
TPS < 1%	79	11.07 [4.86; NC] 24 (30.4)	45	NA [7.62; NC] 9 (20.0)	1.44 [0.65; 3.17]	0.369
TPS ≥ 1%	82	NA 16 (19.5)	41	5.09 [2.10; NC] 16 (39.0)	0.35 [0.17; 0.74]	0.006
Total					Interaction:	0.011[e]

(continued)

Table 15: Subgroups (morbidity, side effects) – RCT, direct comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (continued)

Outcome category Outcome Characteristic Study Subgroup	Pembrolizumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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][b]	p-value[c]
Side effects						
Severe AEs (CTCAE grade ≥ 3)						
PD-L1 expression						
021G						
TPS < 1%	10	12.3 [4.1; NC] 5 (50.0)	13	3.0 [1.7; NC] 7 (53.8)	0.36 [0.10; 1.29][f]	0.117
TPS ≥ 1%	9	2.8 [0.1; 8.5] 7 (77.8)	6	NA [0.3; NC] 3 (50.0)	1.28 [0.32; 5.19][f]	0.728
189						
TPS < 1%	79	5.5 [3.2; NC] 43 (54.4)	45	2.9 [1.9; 3.9] 36 (80.0)	0.52 [0.33; 0.81][f]	0.004
TPS ≥ 1%	82	3.0 [2.1; 4.8] 53 (64.6)	42	3.9 [2.1; 5.8] 28 (66.7)	1.06 [0.67; 1.67][f]	0.812
Total					Interaction:	0.012[e]
TPS < 1%					0.50 [0.33; 0.76][g]	0.001
TPS ≥ 1%					1.08 [0.70; 1.67][g]	0.736

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed
b: Cox proportional hazards model with treatment as covariate, stratified by PD-L1 status, platinum-based chemotherapy and smoking status
c: Two-sided p-value (Wald test)
d: Time to first deterioration; defined as increase of the score by ≥ 10 points compared with baseline.
e: p-value from Q test for heterogeneity.
f: Cox proportional hazards model with treatment as covariate.
g: On the basis of a common data pool of the studies KEYNOTE 189 and KEYNOTE 021G Cox proportional hazards model with treatment as covariate, stratified by study

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio;N: number of analyzed patients; n: number of patients with (at least) one event; 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), 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)

Dyspnoea

In the KEYNOTE 189 study, there was an effect modification by the characteristic "age" for the outcome "dyspnoea". No statistically significant difference between the treatment groups was shown for patients < 65 years, whereas there was a statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy for patients ≥ 65 years.

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

Fatigue

In the KEYNOTE 189 study, there was an effect modification by the characteristic "smoking status" for the outcome "fatigue". A statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy was shown for never smokers. For patients with the smoking status "active" or "former", however, there was no significant statistical difference between the treatment groups.

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

Insomnia

In the KEYNOTE 189 study, there was an effect modification by the characteristic "PD-L1 expression" for the outcome "insomnia". No statistically significant difference between the treatment groups was shown for patients with PD-L1 expression < 1 %, whereas there was a statistically significant difference in favour of pembrolizumab + platinum-based chemotherapy for patients with a PD-L1 expression ≥ 1 %.

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 (arm/shoulder)

In the KEYNOTE 189 study, there are 2 effect modifications for the outcome "pain (arm/shoulder)". On the one hand, there is an effect modification by the characteristic "smoking status", on the other by the characteristic "PD-L1 expression".

For never smokers, a statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy was shown for the characteristic "smoking status". For patients with the smoking status "active" or "former", however, there was no significant statistical difference between the treatment groups. No statistically significant difference between the treatment groups was shown for the characteristic "PD-L1 expression"

for patients with PD-L1 expression < 1 %, whereas there was a statistically significant difference between the treatment groups in favour of pembrolizumab + platinum-based chemotherapy for patients with PD-L1 expression ≥ 1 %.

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

Side effects

Severe AEs (CTCAE grade ≥ 3)

For the outcome "severe AEs (CTCAE grade ≥ 3)", there is an effect modification by the characteristic "PD-L1 expression" based on the meta-analysis of the studies KEYNOTE 189 and KEYNOTE 021G. A statistically significant difference in favour of pembrolizumab + platinum-based chemotherapy was shown for patients with PD-L1 expression < 1 %, whereas there was no statistically significant difference between the treatment groups for patients with a PD-L1 expression ≥ 1 %.

In the dossier, the company presented the effect modification 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 approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 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 whether every outcome considered in the present benefit assessment was non-serious/non-severe or serious/severe. The classification of these outcomes is justified below.

EORTC QLQ-C30 (symptom scales): constipation

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

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

Outcome category **Outcome**	**Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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		
Symptoms (EORTC QLQ-C30 symptom scales)[d, e]		
Dyspnoea	Median: 7.4 vs. 5.1 HR: 0.88 [0.58; 1.35] p = 0.564	Lesser benefit/added benefit not proven
Fatigue	Median: 1.4 vs. 1.4 HR: 0.73 [0.52; 1.03] p = 0.071	Lesser benefit/added benefit not proven
Insomnia	Median: NA vs. 4.1 HR: 0.71 [0.45; 1.12] p = 0.140	Lesser benefit/added benefit not proven
Pain	Median: 5.3 vs. 2.6 HR: 0.77 [0.52; 1.14] p = 0.195	Lesser benefit/added benefit not proven
Appetite loss	Median: 7.2 vs. 6.9 HR: 1.02 [0.66; 1.58] p = 0.917	Lesser benefit/added benefit not proven
Diarrhoea	Median: NA vs. 11.3 HR: 0.92 [0.57; 1.48] p = 0.718	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 2.1 vs. 1.6 HR: 0.94 [0.65; 1.37] p = 0.748	Lesser benefit/added benefit not proven
Constipation	Median: 9.7 vs. 2.5 HR: 0.59 [0.38; 0.90] p = 0.013 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[f]

(continued)

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

Outcome category **Outcome**	**Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Symptoms (EORTC QLQ-LC13 symptom scales)[d, e]		
Dyspnoea	Median: 2.1 vs. 2.6 HR: 1.13 [0.78; 1.61] p = 0.521	Lesser benefit/added benefit not proven
Pain (thorax)	Median: 12.1 vs. 11.8 HR: 1.11 [0.65; 1.91] p = 0.694	Lesser benefit/added benefit not proven
Pain (arm/shoulder)	Median: NA vs. NA HR: 0.75 [0.45; 1.25] p = 0.265	Lesser benefit/added benefit not proven
Pain (other)	Median: 7.6 vs. 3.0 HR: 0.71 [0.46; 1.09] p = 0.116	Lesser benefit/added benefit not proven
Cough	Median: 15.2 vs. 11.5 HR: 1.04 [0.65; 1.67] p = 0.863	Lesser benefit/added benefit not proven
Haemoptysis	Median: NA vs. NA HR: 0.45 [0.16; 1.31] p = 0.144	Lesser benefit/added benefit not proven
Alopecia	Median: 3.1 vs. 11.3 HR: 1.33 [0.85; 2.10] p = 0.215	Lesser benefit/added benefit not proven
Dysphagia	Median: NA vs. 11.8 HR: 0.72 [0.41; 1.26] p = 0.249	Lesser benefit/added benefit not proven
Sore mouth	Median: 7.4 vs. NA HR: 1.21 [0.75; 1.94] p = 0.442	Lesser benefit/added benefit not proven
Neuropathy peripheral	Median: 6.0 vs. 5.1 HR: 0.84 [0.55; 1.29] p = 0.430	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable analyses	Lesser benefit/added benefit not proven

(continued)

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

Outcome category **Outcome**	**Pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Health-related quality of life		
(EORTC QLQ-C30 functional scales)[d, e]		
Global health status	Median: 5.2 vs. 4.1 HR: 1.02 [0.68; 1.52] p = 0.939	Lesser benefit/added benefit not proven
Emotional functioning	Median: 17.7 vs. 12.5 HR: 0.87 [0.55; 1.38] p = 0.555	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 5.5 vs. 3.6 HR: 0.95 [0.64; 1.42] p = 0.809	Lesser benefit/added benefit not proven
Physical functioning	Median: 5.2 vs. 2.9 HR: 0.84 [0.57; 1.23] p = 0.369	Lesser benefit/added benefit not proven
Role functioning	Median: 3.1 vs. 2.7 HR: 0.90 [0.62; 1.33] p = 0.605	Lesser benefit/added benefit not proven
Social functioning	Median: 2.1 vs. 1.9 HR: 0.90 [0.63; 1.30] p = 0.579	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable analyses	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median[g]: 3.9-8.2 vs. 3.0-3.4 HR: 0.74 [0.55; 0.9957] p = 0.047 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Lesser harm, extent: "minor"
Discontinuation due to AEs	Median[g]: NA-16.3 vs. NA-18.3 HR: 1.05 [0.59; 1.87] p = 0.859	Greater/lesser harm not proven
Specific AEs		
Immune-related AEs	Median[g]: NA vs. 16.6 HR: 1.46 [0.69; 3.11] p = 0.320	Greater/lesser harm not proven
Immune-related SAEs	No usable analyses	Greater/lesser harm not proven
Immune-related severe AEs (CTCAE grade ≥ 3)	Median[g]: NA vs. NA HR: 1.82 [0.51; 6.46] p = 0.354	Greater/lesser harm not proven

(continued)

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

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed. 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 CI_u. d: Results on the outcomes "symptoms" and "health-related quality of life" are exclusively based on the KEYNOTE 189 study, since these outcomes were not recorded in KEYNOTE 021G. e: Time to first deterioration. f: The extent of the effect in this non-serious/non-severe outcome was no more than marginal. g: Minimum and maximum proportions of events or quantiles of the time to event or mean changes in each treatment arm in the studies included. 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; VAS: visual analogue scale; 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 the added benefit.

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

Positive effects	**Negative effects**
Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): indication of lesser harm – extent: "minor"	–
a: Consisting of either cisplatin or carboplatin in combination with pemetrexed. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; vs.: versus	

Based on the available analyses, overall assessment showed a positive effect for the outcome "severe AEs (CTCAE grade ≥ 3)", which is not offset by negative effects.

However, since no usable analyses on "overall survival" are available for the relevant subpopulation, an overall conclusion on the added benefit cannot be drawn.

In summary, no added benefit of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy in comparison with cisplatin or carboplatin each in combination with pemetrexed was proven for patients with metastatic non-squamous NSCLC without EGFR or ALK-positive tumour mutations with PD-L1 expression of < 50%.

2.3.4 List of included studies

KEYNOTE 021G

Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF et al. 24-month overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non-small cell lung cancer. J Clin Oncol 2019; 14(1): 124-129.

Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016; 17(11): 1497-1508.

Merck Sharp & Dohme. A study of pembrolizumab (MK-3475) in combination with chemotherapy or immunotherapy in participants with non-small cell lung cancer (MK-3475-021/KEYNOTE-021): study details [online]. In: ClinicalTrials.gov. 30.01.2019 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02039674.

Merck Sharp & Dohme. A study of pembrolizumab (MK-3475) in combination with chemotherapy or immunotherapy in participants with non-small cell lung cancer (MK-3475-021/KEYNOTE-021): study results [online]. In: ClinicalTrials.gov. 30.01.2019 [Accessed: 16.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02039674.

Merck Sharp & Dohme. A phase 1/2 study of MK-3475 (SCH900475) in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic non-small cell lung carcinoma: study P021V03MK3475; clinical study report [unpublished]. 2018.

Merck Sharp & Dohme. Pembrolizumab KEYNOTE 021G trial platinum therapy survey [unpublished]. 2018.

Merck Sharp & Dohme. A phase 1/2 study of MK-3475 (SCH900475) in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic non-small cell lung carcinoma: study P021V03MK3475; Zusatzanalysen [unpublished]. 2018.

KEYNOTE 189

Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378(22): 2078-2092.

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-3475-189/KEYNOTE-189): study details [online]. In: ClinicalTrials.gov. 26.03.2019 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02578680.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of platinum+pemetrexed chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic non-squamous non-small cell lung cancer subjects (KEYNOTE-189) [online]. In: EU Clinical Trials Register. [Accessed: 16.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003694-15 .

Merck Sharp & Dohme. Study of pemetrexed+platinum chemotherapy with or without pembrolizumab (MK-3475) in participants with first line metastatic nonsquamous non-small cell lung cancer (MK-3475-189/KEYNOTE-189): study results [online]. In: ClinicalTrials.gov. 16.03.2019 [Accessed: 16.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02578680.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of platinum+ pemetrexed chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic nonsquamous non-small cell lung cancer subjects (KEYNOTE-189): study P189V01MK3475; clinical study report [unpublished]. 2018.

Merck Sharp & Dohme. TPC survey: Keynote 189 [unpublished]. 2018.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of platinum+ pemetrexed chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic nonsquamous non-small cell lung cancer subjects (KEYNOTE-189): study P189V01MK3475; clinical study report [unpublished]. 2018.

2.4 Research question 2: 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 + platinum-based chemotherapy or on the ACT (status: 24 January 2019)
- bibliographical literature search on pembrolizumab + platinum-based chemotherapy or on the ACT (last search on 8 January 2019)
- search in trial registries for studies on pembrolizumab + platinum-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 + platinum-based chemotherapy or on the ACT (last search on 10 April 2019)

Concurring with the company, the check of the completeness of the study pool identified no relevant RCT on the direct comparison of pembrolizumab + platinum-based chemotherapy in patients with PD-L1 expression ≥ 50% versus pembrolizumab monotherapy as ACT.

The company identified 4 studies for an adjusted indirect comparison based on RCTs. For this indirect comparison presented by the company, no additional relevant studies were identified from the check of the completeness of the study pool.

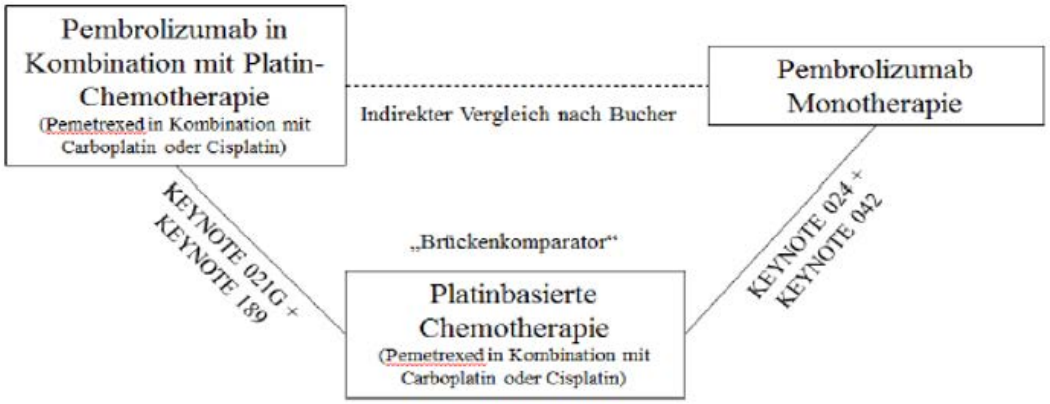
2.4.1.1 Studies included

The company presented an adjusted indirect comparison with the common comparator platinum-based chemotherapy and 2 RCTs on every side of the indirect comparison for the assessment of the added benefit of pembrolizumab + platinum-based chemotherapy in patients with PD-L1 expression ≥ 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 platinum-based chemotherapy) for the drug to be compared, i.e. pembrolizumab + carboplatin-based chemotherapy, as well as for the ACT "pembrolizumab (monotherapy)" in the relevant therapeutic application. The common comparator platinum-based chemotherapy consisting of either cisplatin or carboplatin each in combination with pemetrexed is suitable for the conduction of an adjusted indirect comparison with the included studies listed in Table 18.

Table 18: Study pool – RCT, indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-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)
Intervention vs. common comparator			
KEYNOTE 021G (021G[c])	Yes	Yes	No
KEYNOTE 189 (189[c])	Yes	Yes	No
ACT vs. common comparator			
KEYNOTE 024 (024[c])	Yes	Yes	No
KEYNOTE 042 (042[c])	Yes	Yes	No
a: Consisting of either cisplatin or carboplatin in combination with pemetrexed. b: Study sponsored by the company. c: In the following tables, the study is referred to with this abbreviated form. ACT: appropriate comparator therapy; RCT: randomized controlled trial; vs.: versus			

The study pool concurred with that of the company. Figure 1 shows a schematic representation of the indirect comparison.



Pembrolizumab in Kombination mit Platin-Chemotherapie (Pemetrexerd in Kombination mit Carboplatin oder Cisplatin) = Pembrolizumab in combination with platinum-based chemotherapy (pembrolizumab in combination with carboplatin or cisplatin); Indirekter Vergleich nach Bucher = indirect comparison according to Bucher; Pembrolizumab monotherapy = pembrolizumab monotherapy; “Brückenkomparator” = “common comparator”; Platinum-based chemotherapy (pemetrexed in combination with carboplatin or cisplatin

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

Section 2.3.4 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 + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
Intervention vs. common comparator						
021G	RCT, open-label, parallel	**Cohort G1[c]:** Adults (≥ 18 years) with histologically or cytologically confirmed stage IIIB or IV non-squamous NSCLC without EGFR mutation or ALK translocation and with an ECOG PS ≤ 1, without prior systemic therapy[d]	**Cohort G1[c]:** ▪ Pembrolizumab in combination with carboplatin-based chemotherapy (N = 60) ▪ Carboplatin-based chemotherapy (N = 63) relevant subpopulation thereof[e]: ▪ Pembrolizumab in combination with carboplatin-based chemotherapy (n = 10) ▪ Carboplatin-based chemotherapy (n = 10)	▪ Screening (KEYNOTE 021): up to 28 days before start of treatment ▪ Treatment (cohort G1): until progression, unacceptable side effects, decision by the investigator or the patient, complete response or after maximally 35 cycles of pembrolizumab[f] ▪ Follow-up (cohort G1): outcome-specific[g], at most until death (for the outcome "overall survival")	26 centres in 2 countries: Taiwan and USA **Cohort G1[c]:** 12/2014–ongoing First data cut-off: 08/2016 (prespecified: primary analysis) Second data cut-off: 05/2017 (post hoc: on request of the European Medicines Agency [EMA])	Primary: objective response rate Secondary: overall survival, AEs

(continued)

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
Intervention vs. common comparator						
189	RCT, double-blind, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed stage IV non-squamous NSCLC without EGFR mutation or ALK translocation and with ECOG PS ≤ 1, without prior systemic therapy[d]	▪ Pembrolizumab in combination with platinum-based chemotherapy[h] (N = 410) ▪ Platinum-based chemotherapy[h] (N = 206) relevant subpopulation thereof[e]: ▪ Pembrolizumab in combination with platinum-based chemotherapy[h] (n = 85) ▪ Platinum-based chemotherapy[h] (n = 40)	▪ Screening: up to 28 days before start of treatment ▪ Treatment: until progression, unacceptable side effects, decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[f] ▪ Follow-up: outcome-specific[g], at most until death (for the outcome "overall survival")	143 centres in 16 countries: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Spain, United Kingdom, USA 02/2016–ongoing Data cut-off: 11/2017 (prespecified, first interim analysis) Final analysis planned to take place after approx. 416 deaths	Primary: PFS, overall survival Secondary: Morbidity, symptoms, health-related quality of life, AEs
024	RCT, open-label, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed stage IV NSCLC, PD-L1 expressing tumours (TPS ≥ 50%) without EGFR mutation and without ALK translocation and ECOG PS ≤ 1, without prior systemic therapy[d]	▪ Pembrolizumab (N = 154) ▪ Platinum-based chemotherapy (N = 151) Relevant subpopulation thereof[e, i]: ▪ Pembrolizumab (n = 75) ▪ Platinum-based chemotherapy (n = 74)	▪ Screening: 30 days prior to the start of treatment ▪ Treatment: until progression, unacceptable side effects, study discontinuation due to decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[f] ▪ Follow-up: outcome-specific[g], at most until death (for the outcome "overall survival")	142 centres in 16 countries: Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, United Kingdom, USA 09/2014–05/2016[j]	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

(continued)

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
ACT vs. common comparator						
042	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC, PD-L1 expressing tumours (TPS ≥ 1%) without EGFR mutation or ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[d]	▪ Pembrolizumab (N = 637) ▪ Platinum-based chemotherapy (N = 637) Relevant subpopulation thereof[e, i]: ▪ Pembrolizumab (n = 90) ▪ Carboplatin-based chemotherapy (n = 86)	▪ Screening: 30 days prior to the start of treatment ▪ Treatment: until progression, unacceptable side effects, study discontinuation due to decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[f] ▪ Follow-up: outcome-specific[g], at most until death (for the outcome "overall survival")	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: 04 September 2018	Primary: overall survival Secondary: AE

(continued)

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

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
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: The other cohorts of the KEYNOTE 021 study are not relevant for the assessment.
d: Without prior systemic therapy of the stage IIIB or IV NSCLC (KEYNOTE 021G, KEYNOTE 189 and KEYNOTE 024) or the advanced or metastatic NSCLC stage (KEYNOTE 042)
e: The relevant subpopulation comprised patients with PD-L1 expression ≥ 50% who, pursuant to the results of the TPC survey by the company, had been treated in accordance with the criteria of the pharmaceutical directive for off-label use (Appendix VI to Section K [3]) of carboplatin.
f: Patients in the pembrolizumab arm (KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042) or in both arms (KEYNOTE 189) could temporarily discontinue treatment after confirmed complete response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab at the investigator's discretion ("second course phase") after subsequent confirmed progression (if certain conditions regarding treatment duration and disease status were met). Based on the study documents, it should be assumed that none of the patients (KEYNOTE 189) or only < 5% of the patients in the total study population (KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042) reached the "second course phase".
g: Outcome-specific information is provided in Table 21.
h: Study KEYNOTE 189: cisplatin or carboplatin (determined at the investigator's discretion prior to randomization) + pemetrexed.
i: For the indirect comparison, the study populations of the studies KEYNOTE 024 and KEYNOTE 042 were limited to patients with a metastatic tumour with non-squamous histology and for whom treatment with carboplatin or cisplatin + pemetrexed (KEYNOTE 024) or carboplatin + pemetrexed (KEYNOTE 042) was specified as platinum-based chemotherapy prior to randomization.
j: Since pembrolizumab was superior to platinum-based chemotherapy with respect to overall survival, the study was stopped at the time point of the data cut-off of the second interim analysis (9 May 2016). This second data cut-off was prospectively planned to be performed after 175 events for the outcome "PFS" had been reached. All patients in the treatment arm with exclusively platinum-based chemotherapy had the option to switch to the pembrolizumab arm.

AE: adverse event; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; n: relevant subpopulation; N: number of randomized 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 intervention – RCT, indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Study	Intervention/common comparator	Comparison
Intervention vs. common comparator		
021G 189	▪ See information in Table 7	
ACT vs. common comparator		
024	Pembrolizumab 200 mg IV (infusion administered over 30 minutes) every 3 weeks No change in dosing allowed (according to the SPC)	Platinum-based combination chemotherapy[b] for 4 to 6 cycles: ▪ Cisplatin 75 mg/m^2 IV (infusion administered over 6 to 8 hours) every 3 weeks + pemetrexed 500 mg/m² IV (infusion administered over 10 minutes) every 3 weeks or ▪ Carboplatin 5 or 6 mg/mL/min IV (AUC-dependent, infusion administered over 30 to 60 minutes) every 3 weeks + pemetrexed 500 mg/m² IV (administered as 10-minute infusion) every 3 weeks for at least 4 cycles, followed by continued treatment with pemetrexed every 3 weeks at the investigator's discretion recommended for patients with non-squamous histology. ▪ Administration largely in compliance with the SPCs
	Pretreatment: ▪ chemotherapy and/or radiotherapy as part of neoadjuvant or adjuvant treatment; the last treatment had to be administered at least 6 months prior to the diagnosis of the metastatic disease **Non-permitted pretreatment:** ▪ systemic therapy for stage IV NSCLC **Non-permitted concomitant treatment:** ▪ immunotherapies other than pembrolizumab ▪ other chemotherapies ▪ surgery for symptom and tumour control ▪ live vaccines ▪ corticosteroids except for the treatment of AEs or used as premedication of a platinum-based combination chemotherapy used in the study ▪ bisphosphonates or anti-RANK-L inhibitors	

(continued)

Table 20: Characteristics of the intervention – RCT, indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (continued)

Study	Intervention/common comparator	Comparison
ACT vs. common comparator		
042	Pembrolizumab 200 mg IV as infusion administered over 30 minutes every 3 weeks	Carboplatin-based combination chemotherapy[c] for 4 to at most 6 cycles: ▪ Carboplatin AUC 5 or 6 mg/mL/min IV as infusion administered over 30 to 60 minutes, every 3 weeks, and ▪ pemetrexed 500 mg/m² IV administered as infusion administered over 10 minutes every 3 weeks for at least 4 cycles; for patients with non-squamous histology, this was followed by continued treatment with pemetrexed every 3 weeks at the investigator's discretion and was recommended
	Dose adjustments in case of toxicities ▪ allowed for carboplatin and pemetrexed in line with the SPC ▪ not allowed for pembrolizumab (treatment could be temporarily or permanently 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[d]	

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Before randomization, chemotherapy was chosen on an individual basis from the following platinum-based combination chemotherapies: cisplatin + gemcitabine, cisplatin + pemetrexed, carboplatin + gemcitabine, carboplatin + pemetrexed, carboplatin + paclitaxel. From these options, only cisplatin + pemetrexed and carboplatin + pemetrexed are relevant common comparators for the indirect comparison.
c: Within the framework of the chemotherapy, the following platinum-based combination chemotherapies were chosen on an individual basis prior to randomization: carboplatin + pemetrexed and carboplatin + paclitaxel. From these options, only carboplatin + pemetrexed is a relevant common comparator for the indirect comparison.
d: 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; SPC: Summary of Product Characteristics; vs.: versus

Study design

Studies with the intervention: KEYNOTE 021G and KEYNOTE 189

Since the company used KEYNOTE 021G and KEYNOTE 189 also for the assessment of the added benefit in patients with PD-L1 expression < 50%, these studies are described in Section 2.3.1.2.

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

As already described in the dossier assessment on project A17-06 [9], the KEYNOTE 024 study is a randomized, open-label, controlled study. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation, whose tumours had a PD-L1 expression ≥ 50%. The patients had to be in good general condition (according to an ECOG PS ≤ 1). Prior systemic antineoplastic treatment for the metastatic stage was not allowed.

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based combination chemotherapy (N = 151). The following treatment options were available: cisplatin + gemcitabin, cisplatin + pemetrexed, carboplatin + gemcitabin, carboplatin + pemetrexed or carboplatin + paclitaxel. The treatment suitable for each patient was specified by an investigator on an individual basis prior to randomization. Randomization was stratified by histology (squamous, non-squamous), geographical region (East Asia, not East Asia) and ECOG PS (0, 1).

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.

The administration of pembrolizumab concurred with the requirements of the SPC [4]. The maximum treatment duration for pembrolizumab was 35 cycles. In the KEYNOTE 024 study, no patient in the total study population reached this maximum treatment duration. The platinum-based chemotherapies (cisplatin or carboplatin + pemetrexed) relevant as common comparator for research question 2 were also administered largely in compliance with the respective SPC [5,6] or the Pharmaceutical Directive for off-label use (Appendix VI to Section K [3]) (see below). The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the KEYNOTE 024 study. Thereafter, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended. 46 (37%) patients with non-squamous histology in the treatment arm with solely platinum-based chemotherapy received such maintenance treatment.

Patients were treated until disease progression, occurrence of unacceptable side effects, or discontinuation of the study due to decision by the investigator or the patient. After disease

progression, suitable patients in the comparator arm could switch to monotherapy with pembrolizumab. There was no other limitation regarding subsequent therapies. At the time point of the second interim analysis of 9 May 2016, the proportion of patients with subsequent therapy was 22.7% in the intervention arm and 16.6% in the comparator arm . In the comparator arm, 66 (43.7%) patients had switched to monotherapy with pembrolizumab. Apart from this information, there are no data on subsequent therapies for this data cut-off. Information on the subsequent therapies for the relevant subpopulation is completely missing.

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

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 (≥ 50% vs. 1 to 49%) 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 diagnosis of the metastatic disease. The ECOG PS had to be 0 or 1 in the included patients. 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.

Patients in the intervention arm received pembrolizumab in accordance with the requirements of the SPC [8]. The maximum treatment duration was 35 cycles. In the KEYNOTE 042 study, this maximum treatment duration was only reached by approx. < 5% of the patients in the total study population. Pemetrexed, which was a component of the platinum-based chemotherapy (carboplatin + pemetrexed) relevant as common comparator for research question 2, was also administered in compliance with the requirements of the SPC [5]. Administration of carboplatin was in compliance with the requirements of the SPC [10] or the pharmaceutical directive for off-label use (Appendix VI to Section K [3]) (see below). Patients with non-squamous histology received carboplatin for a maximum of 4 to 6 cycles in the KEYNOTE 042 study. After at least 4 cycles, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended. 196 (52.3%) patients with non-squamous histology in the total population of the KEYNOTE 042 study received such maintenance treatment.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation due to decision by the investigator or the patient.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could receive subsequent therapies. There were no limitations regarding the type of subsequent therapy. The study design did not explicitly 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 entire subpopulation was 37.7% (N = 240) in the intervention arm and 44.0% (N = 280) in the comparator arm (see Table 40 of the full dossier assessment). In the comparator arm, 28 (4.4%) patients had switched to monotherapy with pembrolizumab. There was no information on the subsequent therapies for the relevant subpopulation.

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

Implementation of the Pharmaceutical Directive on the use of carboplatin

Section 2.3.1.2 provides a description of the implementation of the Pharmaceutical Directive on the off-label use of carboplatin in the studies KEYNOTE 189 and KEYNOTE 021G.

As already explained for research question 1 (patients with PPD-L1 expression < 50%) in Section 2.3.1.2, the criteria of Appendix VI to Section K of the Pharmaceutical Directive must be considered for carboplatin treatment in the present therapeutic indication. Neither for the KEYNOTE 024 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 on 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.

Relevant subpopulations for research question 2 (PD-L1 expression ≥ 50 %)

One subpopulation of each of the included studies was also relevant for research question 2. In the studies KEYNOTE 189 and KEYNOTE 021G as well as KEYNOTE 024 and KEYNOTE 042, these were patients with metastatic non-squamous NSCLC and PD-L1 expression ≥ 50%. Moreover, as with research question 1, the patients with carboplatin as treatment component had have to be treated in compliance with the requirements of the Pharmaceutical Directive for

off-label use. A further limitation of the study populations for the KEYNOTE 024 and KEYNOTE 042 studies results from the available common comparator consisting of either cisplatin or carboplatin in combination with pemetrexed, as described in Section 2.4.1.1 In its dossier, the company presented corresponding analyses for these subpopulations for the four studies KEYNOTE 189 and KEYNOTE 021G as well as KEYNOTE 024 and KEYNOTE 042. Overall, 470 patients from the 4 studies (pembrolizumab + platinum-based chemotherapy: 95; pembrolizumab monotherapy: 165; common comparator [platinum-based chemotherapy]: 210) were included in the assessment.

Data cut-offs

Of all 4 studies (KEYNOTE 021G and KEYNOTE 189 as well as KEYNOTE 024 and KEYNOTE 042), those data cut-offs for which the company had processed the data in Module 4 were used.

For the studies KEYNOTE 189, 021G and 024, the respective decision of the company for a data cut-off is comprehensible. Since the company used the same data cut-offs of the KEYNOTE 021G and KEYNOTE 189 studies for research question 2 as it had used for research question 1, explanations on these data-cut offs can be found in Section 2.3.1.2. The data cut-off from KEYNOTE 024 is the second interim analysis of 9 May 2016. After this data cut-off, all patients in the comparator arm had the option to switch to monotherapy with pembrolizumab due to the superiority of pembrolizumab in “overall survival”. The company used the second interim analysis of the KEYNOTE 042 study 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. The company presents the final analyses after approx. 45 months following the start of the study on 4 September 2018, however, it conducts no indirect comparison with the effect estimations. The analyses on the basis of the data cut-off of 26 February 2018 are used for the benefit assessment, since the analyses for the data cut-off of 4 September 2018 are not completely available for the indirect comparison.

Table 21 shows the planned duration of follow-up observation of the patients for the individual outcomes.

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
Intervention vs. common comparator	
021G	see information in Table 8
189	
ACT vs. common comparator	
024	
Mortality	
Overall survival	▪ After the end of treatment (except for progression): every 3 months until progression ▪ After progression or initiation of a new antineoplastic treatment: every 2 months until death
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13)	▪ Until 30 days after the last dose of the study medication ▪ At the end of treatment before progression: every 9 weeks until progression or initiation of new antineoplastic treatment
Health status (EQ-5D VAS)	▪ Until 30 days after the last dose of the study medication ▪ At the end of treatment before progression: every 9 weeks until progression or initiation of new antineoplastic treatment
Health-related quality of life (EORTC QLQ-C30)	▪ Until 30 days after the last dose of the study medication ▪ At the end of treatment before progression: every 9 weeks until progression or initiation of new antineoplastic treatment
Side effects	
AEs	▪ Until 30 days after the last dose of the study medication
SAEs and immune-related AEs	▪ 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 was initiated, whichever occurred first)
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 initiation of a new antineoplastic treatment (whichever occurred first)

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.

ACT: appropriate comparator therapy; AE: adverse event; EORTC: European Organization 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; VAS: visual analogue scale; vs.: versus

In each of the four studies KEYNOTE 021G, KEYNOTE 189, KEYNOTE 024 and KEYNOTE 042, observation periods for the outcomes “morbidity” and “health-related quality of life” (if recorded) as well as “side effects” were systematically shortened, since they were only recorded for the duration of the 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.

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 + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Study	021G		189		024		042	
Data cut-off Characteristics Category	Pembrolizumab + carboplatin-based chemotherapy	Carboplatin-based chemotherapy	Pembrolizumab + platinum-based chemotherapy[a]	Platinum-based chemotherapy[a]	Pembrolizu-mab	Platinum-based chemotherapy[a]	Pembrolizu-mab	Carboplatin-based chemotherapy
	N[b] = 10	N[b] = 10	N[b] = 85	N[b] = 40	N[b] = 75	N[b] = 74	N[b] = 90	N[b] = 86
Age [years], mean (SD)	63 (9)	66 (6)	64 (9)	65 (9)	64 (10)	64 (10)	62 (11)	63 (10)
Sex [F/M], %	80/20	30/70	32/68	55/45	43/57	36/64	38/62	45/55
Ethnicity, n (%)								
White	7 (70.0)	10 (100.0)	82 (96.5)	39 (97.5)	60 (80.0)	56 (75.7)	55 (61.1)	53 (61.6)
Non-white	2 (20.0)	0 (0)	3 (3.5)	0 (0)	15 (20.0)	18 (24.3)	35 (38.9)	33 (38.4)
Unknown	1 (10.0)	0 (0)	0 (0)	1 (2.5)	–	–	–	–
Region, n (%)								
EU	ND	ND	56 (65.9)	24 (60.0)	42 (56.0)	40 (54.1)	23 (25.6)	15 (17.4)
Non-EU	ND	ND	29 (34.1)	16 (40.0)	33 (44.0)	34 (45.9)	67 (74.4)	71 (82.6)
Smoking status, n (%)								
Never-smoker	4 (40.0)	0 (0)	12 (14.1)	5 (12.5)	3 (4.0)	11 (14.9)	22 (24.4)	28 (32.6)
Former	6 (60.0)	10 (100.0)	54 (63.5)	25 (62.5)	57 (76.0)	49 (66.2)	57 (63.3)	51 (59.3)
Active	0 (0)	0 (0)	19 (22.4)	10 (25.0)	15 (20.0)	14 (18.9)	11 (12.2)	7 (8.1)
ECOG PS, n (%)								
0	3 (30.0)	3 (30.0)	44 (51.8)	15 (37.5)	24 (32.0)	26 (35.1)	26 (28.9)	27 (31.4)
1	7 (70.0)	7 (70.0)	41 (48.2)	25 (62.5)	50 (66.7)	48 (64.9)	64 (71.1)	59 (68.6)
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	–	–	–	–	1 (1.3)	–	–	–

(continued)

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

Study	021G		189		024		042	
Data cut-off Characteristics Category	Pembrolizumab + carboplatin-based chemotherapy	Carboplatin-based chemotherapy	Pembrolizumab + platinum-based chemotherapy[a]	Platinum-based chemotherapy[a]	Pembrolizu-mab	Platinum-based chemotherapy[a]	Pembrolizu-mab	Carboplatin-based chemotherapy
	N[b] = 10	N[b] = 10	N[b] = 85	N[b] = 40	N[b] = 75	N[b] = 74	N[b] = 90	N[b] = 86
Disease stage, n (%)								
IIIB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.4)	ND	ND
IV	10 (100.0)	10 (100.0)	85 (100.0)	40 (100.0)	75 (100.0)	73 (98.6)	90 (100)c	86 (100)[c]
Metastases, n (%)								
M0	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.4)	0 (0)	0 (0)
M1	1 (10.0)	1 (10.0)	0 (0)	0 (0)	9 (12.0)	12 (16.2)	32 (35.6)	43 (50.0)
M1A	2 (20.0)	1 (10.0)	0 (0)	0 (0)	25 (33.3)	22 (29.7)	19 (21.1)	16 (18.6)
M1B	7 (70.0)	8 (80.0)	29 (34.1)	9 (22.5)	41 (54.7)	39 (52.7)	39 (43.3)	27 (31.4)
MX	0 (0)	0 (0)	56 (65.9)	31 (77.5)	0 (0)	0 (0)	0 (0)	0 (0)
Time since initial diagnosis [months]								
Mean (SD)	4.6 (9.0)	2.4 (0.7)	4.6 (10.0)	4.1 (8.9)	5.5 (11.3)	5.4 (26.7)	6.0 (15.4)	3.4 (6.7)
Median [min; max]	1.7 [0.8; 30.0]	2.3 [1.4; 3.4]	1.5 [0.5; 67.0]	1.4 [0.3; 44.4]	1.7 [0.7; 58.8]	1.6 [0.5; 230.8]	1.5 [0.1; 115.7]	1.6 [0.4; 42.3]
Tumour size at start of the study [mm]								
Mean (SD)	74.8 (41.5)	83.0 (42.2)	102.3 (61.6)	108.3 (57.4)	94.6 (58.2)	95.2 (55.0)	101.7 (57.7)	101.6 (59.3)
Median [min; max]	64.0 [35.0; 156.0]	70.5 [31.0; 137.0]	90.5 [14.8; 270.7]	102.4 [22.2; 239.3]	82.0 [16.0; 322.0]	84.0 [17.0; 266.0]	90.4 [14.6; 267.4]	97.2 [18.5; 324.0]

(continued)

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

Study	021G		189		024		042	
Data cut-off **Characteristics** **Category**	**Pembrolizumab + carboplatin-based chemotherapy**	**Carboplatin-based chemotherapy**	**Pembrolizumab + platinum-based chemotherapy[a]**	**Platinum-based chemotherapy[a]**	**Pembrolizu-mab**	**Platinum-based chemotherapy[a]**	**Pembrolizu-mab**	**Carboplatin-based chemotherapy**
	N[b] = 10	**N[b] = 10**	**N[b] = 85**	**N[b] = 40**	**N[b] = 75**	**N[b] = 74**	**N[b] = 90**	**N[b] = 86**
Brain metastases, n (%)								
Yes	2 (20.0)	0 (0)	14 (16.5)	10 (25.0)	8 (10.7)	5 (6.8)	7 (7.8)	6 (7.0)
No	8 (80.0)	10 (100.0)	71 (83.5)	30 (75.0)	67 (89.3)	69 (93.2)	83 (92.2)	80 (93.0)
Histology, n (%)								
Adenocarcinoma	9 (90.0)	8 (80.0)	81 (95.3)	38 (95.0)	64 (85.3)	65 (87.8)	83 (92.2)	74 (86.0)
Not further specified	1 (10.0)	2 (20.0)	3 (3.5)	1 (2.5)	6 (8.0)	2 (2.7)	1 (1.1)	5 (5.8)
Other	0 (0)	0 (0)	1 (1.2)	1 (2.5)	5 (6.7)	7 (9.5)	6 (6.7)	7 (8.1)
prior therapies, n (%)								
Adjuvant prior therapy	0 (0)	0 (0)	adjuvant/neo-adjuvant:		3 (4.0)	0 (0.0)	3 (3.3)	1 (1.2)
Neoadjuvant prior therapy	0 (0)	0 (0)	8 (9.4)	2 (5.0)	3 (4.0)	1 (1.4)	1 (1.1)	2 (2.3)
platinum-based chemotherapy, n (%)								
Cisplatin	–	–	30 (35.3)	15 (37.5)	46 (61.3)	37 (50.0)	–	–
Carboplatin	10 (100)	10 (100)	55 (64.7)	25 (62.5)	29 (38.7)	37 (50.0)	90 (100)[d]	86 (100)[d]
Treatment discontinuation, n (%)	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]
Study discontinuation, n (%)	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]	ND[e]

(continued)

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

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c: According to the company, the relevant subpopulation was limited to patients with stage IV disease.
d: The company limited the relevant subpopulation to patients allocated to treatment with carboplatin + pemetrexed prior to randomization.
e: There was no information on treatment and study discontinuations for the relevant subpopulation.
ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients of the relevant subpopulation; ND: no data; RCT: randomized controlled trial; SD: standard deviation;; vs.: versus

Overall, the characteristics of the relevant subpopulations are sufficiently comparable both between the studies KEYNOTE 021G, KEYNOTE 189, KEYNOTE 024 and KEYNOTE 042 and each between the two treatment arms in the individual studies. The mean age of the included patients in the relevant subpopulation of the studies KEYNOTE 021G, KEYNOTE 189, KEYNOTE 024 and KEYNOTE 042 was 64 years; almost the majority of them was male and white. Almost all patients had stage IV disease and most of them had no brain metastases. The mean period elapsed since the initial diagnosis was about 5 years.

The major difference between the studies is due to the different treatment options within the framework of the platinum-based chemotherapy. In the studies KEYNOTE 189 and KEYNOTE 024 approx. 35% to 60% of the patients in the relevant subpobulation received cisplatin and the other patients received carboplatin. All patients of the relevant subpopulations of the studies KEYNOTE 021G and KEYNOTE 042 received carboplatin. Another difference between the studies is the fact that on average approx. 74% of the patients in the total study population with non-squamous histology in KEYNOTE 021G and KEYNOTE 189 had received maintenance treatment with pemetrexed (KEYNOTE 021G: N = 92 [76.0%]; KEYNOTE 189: N = 445 [73.3%]). 46 (37%) patients or 196 (52%) patients with non-squamous histology in the studies KEYNOTE 024 and KEYNOTE 042 received such maintenance treatment. There was no information for the relevant subpopulation. Moreover, there is a difference regarding the characteristic “region”: in KEYNOTE 042, the proportion of patients from non-EU countries is clearly higher than in the studies KEYNOTE 189 and KEYNOTE 024. Information on the study KEYNOTE 021G is missing.

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: Information on the course of the study – RCT, indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + platinum-based chemotherapy[a]**	**Platinum-based chemotherapy[a]**
Intervention vs. common comparator		
021G	N = 10	N = 10
Treatment duration [months]		
Median [min; max]	8.8 [3.5; 24.6]	3.7 [0.6; 13.1]
Mean (SD)	12.6 (8.5)	5.1 (4.5)
Observation period [months]		
Overall survival		
Median [min; max]	19.7 [10.7; 24.8]	18.9 [2.4; 24.1]
Mean (SD)	19.2 [5.0]	16.8 (6.5)
Morbidity	Not recorded	
Health-related quality of life	Not recorded	
Side effects (SAEs)	No usable data	
189	N = 84	N = 38
Treatment duration [months]		
Median [min; max]	9.0 [0.0; 19.0]	4.4 [0.0; 19.1]
Mean (SD)	9.0 (5.0)	5.6 (4.8)
Observation period [months]		
Overall survival		
Median [min; max]	11.5 [0.3; 19.4]	8.8 [0.4; 19.2]
Mean (SD)	11.6 (4.4)	9.2 (5.0)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (SAEs)	No usable data	

(continued)

Table 23: Information on the course of the study – RCT, indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (continued)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab**	**Platinum-based chemotherapy[a]**
ACT vs. common comparator		
024	N = 75	N = 73
Treatment duration [months]		
Median [min; max]	7.1 [0.0; 18.7]	3.5 [0.0; 14.1]
Mean (SD)	7.0 (5.2)	4.3 (3.8)
Observation period [months]		
Overall survival		
Median [min; max]	9.7 [0.1; 18.9]	8.6 [0.0; 15.3]
Mean (SD)	9.4 (4.5)	8.2 (3.8)
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (SAEs)	No usable data	
042	N = 90	N = 79
Treatment duration [months]		
Median [min; max]	5.3 [0.0; 26.6]	5.7 [0.0; 28.6]
Mean (SD)	8.1 (7.6)	7.5 (6.7)
Observation period [months]		
Overall survival		
Median [min; max]	14.8 [0.3; 34.2]	13.6 [0.3; 38.1]
Mean (SD)	15.1 (8.9)	14.1 (8.8)
Morbidity	Not recorded	
Health-related quality of life	Not recorded	
Side effects (SAEs)		
Median [min; max]	7.9 [0.3; 29.6]	
Mean (SD)	10.5 (7.9)	

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed

ACT: appropriate comparator therapy; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SAEs: serious adverse events; SD: standard deviation; vs.: versus

In the studies KEYNOTE 021G, KEYNOTE 189 and KEYNOTE 024, treatment duration in the intervention arm was about twice as long as in the comparator arm; only in the KEYNOTE 042 study, treatment duration was almost equal in both arms. The observation period for the outcome "overall survival" was balanced between the arms in the individual studies. However, the observation period for "overall survival" clearly differed between the studies (from approx. 9 months to approx. 20 months). For the intervention and the comparator arm, information on the observation periods is lacking for the outcomes "morbidity", "health-related quality of life" as well as for the outcomes of the category "side effects". The data on the observation period

of SAEs provided by the company in its dossier are not usable, since patients who switched from the treatment arm with exclusively platinum-based chemotherapy to monotherapy with pembrolizumab were only considered until the time point of the treatment switch (see Section 2.3.1.2). Moreover, the company presented no data on the reasons for the treatment discontinuation for the relevant subpopulation.

For those outcomes for which data on observation periods are missing, it is assumed that there is a similarly large difference in observation periods between the treatment arms as in the treatment duration of the respective study, as their follow-up was limited (see Table 21 for planned follow-up).

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 to the described differences between the studies KEYNOTE 021G and KEYNOTE 189 as well as KEYNOTE 024 and KEYNOTE 042. However, possible impacts of these differences have to be investigated for the individual outcomes.

Treatment switch from the treatment arm with exclusively platinum-based chemotherapy to monotherapy with pembrolizumab after disease progression

As described in Sections 2.3.1.2 and 2.4.1.2, suitable patients in the studies KEYNOTE 021G, KEYNOTE 189 and KEYNOTE 024 could switch from the treatment arm with exclusively platinum-based chemotherapy to monotherapy with pembrolizumab after disease progression in line with the protocol. This treatment was approved for patients with PD-L1 expression ≥ 1% (and thus for the subpopulations relevant for research question 2) [4,11]. In the KEYNOTE 042 study 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 patients from the KEYNOTE 042 study had switched to various subsequent therapies at the data cut-off of 26 February 2018 (see Section 2.4.1.2).

In all four studies, relevant proportions of patients in the relevant subpopulation had already switched from the treatment arm with exclusively platinum-based chemotherapy to treatment with pembrolizumab as monotherapy at the data cut-offs used for the benefit assessment: In the KEYNOTE 021G study, these were 4 (40%), in KEYNOTE 189 it were 11 (27.5%), in the study KEYNOTE 024 it were 28 (37.8%) and in KEYNOTE 042 it were 16 patients (18.6%). Data on further data cut-offs for the relevant subpopulations are missing. The company did not present Kaplan-Meier curves on the time to treatment switch for patients with PD-L1 expression ≥ 50% (research question 2).

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

As described in research question 1, the results of the outcome “overall survival” presented by the company are not interpretable due to contradictory data of the company in its dossier on

pembrolizumab in NSCLC (Module 4 B on non-squamous NSCLC and Module 4 C on squamous NSCLC). This is explained below.

When describing the operationalizations of the outcome "overall survival" for the studies KEYNOTE 407 and KEYNOTE 042 in its dossier on squamous NSCLC (Module 4 C), 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 corresponding result tables indicate that the observation was censored at the time point of the data cut-off. These contradictory data also apply to the KEYNOTE 042 study, which the company included in both its dossier on squamous NSCLC (Module 4 C) and its dossier on non-squamous NSCLC (Module 4 B) (see research question 2). In its dossier on non-squamous NSCLC (Module 4 B), the company did not state that patients were censored at the time point of the treatment switch. However, it neither stated that the patients who had switched to monotherapy with pembrolizumab had not been censored. When describing the risk of bias for the studies on direct comparison in its dossier on non-squamous NSCLC (Module 4 B), the company moreover stated that it was going to consider the treatment switch of the patients in the analysis methods at outcome level. It remains unclear, however, what it refers to in this context.

In the study documents of the studies KEYNOTE 021G and KEYNOTE 189 as well as KEYNOTE 024 and KEYNOTE 042, "overall survival" was operationalized as period between randomization and death for any reason. As in Module 4 C on squamous NSCLC, the result tables of Module 4 B on non-squamous NSCLC indicate in connection with the ITT analyses that the observation was censored at the time point of the data cut-off.

Overall, 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 + platinum-based chemotherapy[a] vs. platinum-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			
Intervention vs. common comparator							
021G	Yes	Yes	No	No	Yes	Yes	Low
189	Yes	Yes	Yes	Yes	Yes	Yes	Low
ACT vs. common comparator							
024	Yes	Yes	No	No	Yes	Yes	Low
042	Yes	Yes	No	No	Yes	Yes	Low
a: Consisting of either cisplatin or carboplatin in combination with pemetrexed ACT: appropriate comparator therapy; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for all 4 studies. This concurs with the company's assessment.

Limitations resulting from the open-label study design for the studies KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042 are described in Section 2.3.2 with the outcome-specific risk of bias.

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
  - Overall survival
- 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 concurred with that of the company. However, in its dossier, the company presented further outcomes as supplementary information (see Section 2.6.4.3 of the full dossier assessment), whose results it still cited for the derivation of the added benefit (see Section 2.6.8.2 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 + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

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											
021G	No[b]	No[c]	No[c]	No[c]	No[b]	Yes	Yes	No[b]	No[b]	No[b]	No[b]
189	No[b]	Yes	No[b]	Yes	No[b]	Yes	Yes	Yes	No[b]	Yes	No[b]
ACT vs. common comparator											
024	No[b]	Yes	No[b]	Yes	No[b]	Yes	Yes	No[b]	No[b]	No[b]	No[b]
042	No[b]	No[c]	No[c]	No[c]	No[b]	Yes	Yes	No[b]	No[b]	No[b]	No[b]

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed
b: No usable data available for the relevant subpopulation; for reasons, see Section 2.4.1.2 as well as Sections 2.6.5.2 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 Organization 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; VAS: visual analogue scale; vs.: versus

2.4.2.2 Risk of bias

Table 26 describes the risk of bias for the results of the relevant outcomes.

Table 26: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: pembrolizumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]

Study	Study level	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												
021G	L	–[b]	–[c]	–[c]	–[c]	–[b]	H[d]	H[e]	–[b]	–[b]	–[b]	–[b]
189	L	–[b]	H[f]	–[b]	H[f]	–[b]	L[g]	H[e]	H[e]	–[b]	H[e]	–[b]
ACT vs. common comparator												
024	L	–[b]	H[d]	–[b]	H[d]	–[b]	H[d]	H[e]	–[b]	–[b]	–[b]	–[b]
042	L	–[b]	–[c]	–[c]	–[c]	–[b]	H[d]	H[e]	–[b]	–[b]	–[b]	–[b]

a: Consisting of either cisplatin or carboplatin in combination with pemetrexed.
b: No usable data available for the relevant subpopulation; for reasons, see Section 2.4.1.2 as well as Sections 2.6.5.2 and 2.6.5.3.2 of the full dossier assessment.
c: Outcome not recorded.
d: Lack of blinding in subjective recording of outcomes.
e: Missing data on the observation period for the intervention arm and the control arm.
f: Large differential proportion of patients (> 5 percentage points) in the relevant subpopulation who were not considered in the analysis; decreasing response to questionnaires in the relevant subpopulation over the course of the study.
g: Despite the low risk of bias, a restricted certainty of results was assumed for the outcome "discontinuation due to AEs" (see Section 2.6.5.2 of the full dossier assessment).

ACT: appropriate comparator therapy; 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; QLQ-C30: Quality of Life Questionnaire - Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Usable analyses on the outcomes "overall survival", "SAEs", "immune-related SAEs" and on further specific AEs are missing for the four studies included (see Section 2.4.1.2 as well as Sections 2.6.5.2 and 2.6.5.3.2 of the full dossier assessment). This also applies to the immune-related AEs and immune-related severe AEs (CTCAE grade ≥ 3) in the studies KEYNOTE

021G, KEYNOTE 024 and KEYNOTE 042. “Health status” was not recorded in the studies KEYNOTE 021G and KEYNOTE 042, usable analyses on “health status” are not available for the studies KEYNOTE 189 and KEYNOTE 024 (see Section 2.6.4.3.2 of the full dossier assessment). Therefore, the risk of bias was not assessed for these outcomes. There is a high risk of bias for all other outcomes of the four studies (KEYNOTE 021G, KEYNOTE 189, KEYNOTE 024 and KEYNOTE 042), except for the outcome “discontinuation due to AEs” in the study KEYNOTE 189. This is justified below.

The risk of bias for the outcomes on symptoms and health-related quality of life from the KEYNOTE 189 study was rated as potentially high, because high differential proportions of patients had not been considered in the analyses. Moreover, the number of returned questionnaires decreased in the course of the studies. The risk of bias for the outcomes on symptoms and health-related quality of life from KEYNOTE 024 was rated as potentially high due to lack of blinding in subjective recording of outcomes.

Thus, no hint of added benefit can be derived for the outcomes on symptoms and health-related quality of life, since only results from 1 study with a high bias potential are available on each side of the indirect comparison.

Due to the open-label study design , the results of the outcome “discontinuation due to AEs” were rated as potentially highly biased in the studies KEYNOTE 021G, KEYNOTE 024 and KEYNOTE 042. In the KEYNOTE 189 study, the certainty of conclusions for this outcome was restricted despite the low risk of bias (see Section 2.6.4.2 of the full dossier assessment).

Due to the lacking or unusable data on the observation period, the risk of bias for the outcomes “severe AEs (CTCAE grade ≥ 3)” (all four studies), “immune-related AEs” (only KEYNOTE 189) and “immune-related severe AEs (CTCAE grade ≥ 3)” (only KEYNOTE 189) was rated as high. It could not be assessed whether a relevant number of incomplete observations due to potentially informative reasons was existent (see Section 2.6.4.2 of the full dossier assessment).

The company rated the risk of bias of the results on all outcomes, except for the results on the outcomes on symptoms and health-related quality of life from the KEYNOTE 024 study as low.

2.4.2.3 Results

Overall consideration of the available data for the indirect comparison results in the following picture:

There are no usable data for the outcomes of the categories “mortality”, “morbidity” and “health-related quality of life” or the outcomes were not recorded in the studies. In the indirect comparison, usable analyses were only available for the outcomes "severe AEs (CTCAE grade ≥ 3)” and "discontinuation due to AEs". Therefore, the present data situation does not permit a benefit assessment with subsequent weighing of positive and negative effects for the indirect comparison despite the general suitability of the studies KEYNOTE 021G, KEYNOTE 189,

KEYNOTE 024 and KEYNOTE 042. Overall, the data presented by the company for indirect comparison are not suitable for deriving an added benefit of pembrolizumab + platinum-based chemotherapy as first-line treatment of adults with metastatic non-squamous NSCLC without EGFR or ALK-positive mutations with a PD-L1 expression ≥ 50% in comparison with the ACT. This resulted in no hint of an added benefit of pembrolizumab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company presented no usable data for the assessment of the added benefit of pembrolizumab + platinum-based chemotherapy in patients with metastatic non-squamous NSCLC without EGFR or ALK-positive mutations with PD-L1 expression ≥ 50%, an added benefit of pembrolizumab + platinum-based chemotherapy is not proven for these patients.

2.4.4 List of included studies

KEYNOTE 021G

Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF et al. 24-month overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non-small cell lung cancer. J Thorac Oncol 2019; 14(1): 124-129.

Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016; 17(11): 1497-1508.

Merck Sharp & Dohme. A study of pembrolizumab (MK-3475) in combination with chemotherapy or immunotherapy in participants with non-small cell lung cancer (MK-3475-021/KEYNOTE-021): study details [online]. In: ClinicalTrials.gov. 30.01.2019 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02039674.

Merck Sharp & Dohme. A study of pembrolizumab (MK-3475) in combination with chemotherapy or immunotherapy in participants with non-small cell lung cancer (MK-3475-021/KEYNOTE-021): study results [online]. In: ClinicalTrials.gov. 30.01.2019 [Accessed: 16.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02039674.

Merck Sharp Dohme. A phase 1/2 study of MK-3475 (SCH900475) in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic non-small cell lung carcinoma: study P021V03MK3475; clinical study report [unpublished]. 2018.

Merck Sharp Dohme. Pembrolizumab KEYNOTE 021G trial platinum therapy survey [unpublished]. 2018.

Merck Sharp Dohme. A phase 1/2 study of MK-3475 (SCH900475) in combination with chemotherapy or immunotherapy in patients with locally advanced or metastatic non-small cell lung carcinoma: study P021V03MK3475; Zusatzanalysen [unpublished]. 2018.

KEYNOTE 189

Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 378(22): 2078-2092.

Merck Sharp & Dohme. Study of pemetrexed+platinum chemotherapy with or without pembrolizumab (MK-3475) in participants with first line metastatic nonsquamous non-small cell lung cancer (MK-3475-189/KEYNOTE-189): study details [online]. In: ClinicalTrials.gov. 26.03.2019 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02578680.

Merck Sharp & Dohme. A randomized, double-blind, phase III study of platinum+pemetrexed chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic non-squamous non-small cell lung cancer subjects (KEYNOTE-189) [online]. In: EU Clinical Trials Register. [Accessed: 16.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003694-15.

Merck Sharp & Dohme. Study of pemetrexed+platinum chemotherapy with or without pembrolizumab (MK-3475) in participants with first line metastatic nonsquamous non-small cell lung cancer (MK-3475-189/KEYNOTE-189): study results [online]. In: ClinicalTrials.gov. 16.03.2019 [Accessed: 16.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02578680.

Merck Sharp Dohme. A randomized, double-blind, phase III study of platinum+ pemetrexed chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic nonsquamous non-small cell lung cancer subjects (KEYNOTE-189): study P189V01MK3475; clinical study report [unpublished]. 2018.

Merck Sharp Dohme. TPC survey: Keynote 189 [unpublished]. 2018.

Merck Sharp Dohme. A randomized, double-blind, phase III study of platinum+ pemetrexed chemotherapy with or without pembrolizumab (MK-3475) in first line metastatic nonsquamous non-small cell lung cancer subjects (KEYNOTE-189): study P189V01MK3475; Zusatzanalysen [unpublished]. 2018.

KEYNOTE 024

Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A et al. Health-related quality of life for pembrolizumab vs chemotherapy in advanced nsclc with PD-L1 TPS >=50%: data from Keynote-024. J Thorac Oncol 2017; 12(1 Suppl): S8-S9.

Huang M, Pietanza MC, Samkari A, Pellissier J, Burke T, Chandwani S et al. Q-TWiST analysis to assess benefit-risk of pembrolizumab in patients with PD-L1-positive advanced or metastatic non-small cell lung cancer. Pharmacoeconomics 2018; 37(1): 105–116

Merck S, Dohme C. Pembrolizumab KEYNOTE 024 trial platinum therapy survey. 2016.

Merck Sharp & Dohme. Study of pembrolizumab (MK-3475) compared to platinum-based chemotherapies in participants with metastatic non-small cell lung cancer (MK-3475-024/KEYNOTE-024): study details [online]. In: ClinicalTrials.gov. 15.02.2019 [Accessed: 16.05.2019]. URL: https://ClinicalTrials.gov/show/NCT02142738.

Merck Sharp & Dohme. A randomized open-label phase III trial of MK-3475 versus platinum based chemotherapy in 1L subjects with PD-L1 strong metastatic non-small cell lung cancer [online]. In: EU Clinical Trials Register. [Accessed: 16.05.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-000323-25.

Merck Sharp & Dohme. Study of pembrolizumab (MK-3475) compared to platinum-based chemotherapies in participants with metastatic non-small cell lung cancer (MK-3475-024/KEYNOTE-024): study results [online]. In: ClinicalTrials.gov. 15.02.2019 [Accessed: 16.05.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02142738.

Merck Sharp Dohme. A randomized open-label phase III trial of pembrolizumab versus platinum based chemotherapy in first-line subjects with PD-L1 strong metastatic non-small cell lung cancer (NSCLC): study KEYNOTE 024 (P024V01MK3475); clinical study report [unpublished]. 2016.

Merck Sharp Dohme. A randomized open-label phase III trial of pembrolizumab versus platinum based chemotherapy in first-line subjects with PD-L1 strong metastatic non-small cell lung cancer (NSCLC): study KEYNOTE 024 (P024V01MK3475); Zusatzanalysen [unpublished]. 2016.

Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016; 375(19): 1823-1833.

KEYNOTE 042

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.

2.5 Probability and extent of added benefit – summary

Table 27 summarizes the results of the assessment of the added benefit of pembrolizumab + platinum-based chemotherapy in comparison with the ACT.

Table 27: Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects within the framework of a combination therapy; see also Appendix VI to Section K of the Pharmaceutical Directive [3]) *or* ▪ carboplatin in combination with nab-paclitaxel	Added benefit not proven
First-line treatment of metastatic non-squamous NSCLC without EFGR or ALK-positive tumour mutations in adults with PD-L1 expression ≥ 50%[b]	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: For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1

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

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 Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use) [online]. 05.01.2019 [Accessed: 25.02.2019]. URL: https://www.g-ba.de/downloads/83-691-518/AM-RL-VI-Off-label-2019-01-05.pdf.

4. Merck Sharp Dohme. NL-Haarlem: Fachinformation Keytruda (Pembrolizumab) 50 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung. Stand: März. 2019.

5. Eli Lilly Nederland. Fachinformation ALIMTA (Pemetrexed) 100 mg und 500 mg Pulver zur Herstellung eines Konzentrates zur Herstellung einer Infusionslösung; Stand: Februar. 2018.

6. Hexal. Fachinformation Cisplatin NeoCorp 1 mg/ml Konzentrat zur Herstellung einer Infusionslösung; Stand: Dezember. 2015.

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

8. MSD Sharp & Dohme. KEYTRUDA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 04.2019 [Accessed: 17.04.2019]. 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. Schrijvers D. Treatment of advanced cancer. In: Catane R, Cherny NI, Kloke M, Tanneberger S, Schrijvers D (Ed). Handbook of advanced cancer care. London: Taylor & Francis Group; 2006. S. 1-4.

11. Mahner S, Wölber L, Hilpert F, Baumann K, Kommoss S, De Gregorio N et al. Innovationen in der medikamentösen Therapie des Ovarialkarzinoms. Gynakologe 2014; 47(12): 942-950.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2019/a19-30-pembrolizumab-nichtplattenepitheliales-nicht-kleinzelliges-lungenkarzinom-nutzenbewertung-gemaess-35a-sgb-v.11926.html.