IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A17-06

# Pembrolizumab (non-small cell lung cancer) –

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

## Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Pembrolizumab (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 May 2017). 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-small cell lung cancer) – Benefit assessment according to §35a Social Code Book V

**Commissioning agency:**

Federal Joint Committee

**Commission awarded on:**

10 February 2017

**Internal Commission No.:**

A17-06

**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:**

- Jochem Potenberg, Waldkrankenhaus Protestant Hospital, Berlin, 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[2]:**

- Daniela Preukschat
- Christiane Balg
- Wolfram Groß
- Simone Johner
- Ulrike Lampert
- Sonja Schiller
- Christoph Schürmann
- Beate Wieseler

**Keywords:** pembrolizumab, carcinoma – non-small-cell lung, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

# Table of contents

## List of tables[3]

**Page**



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

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| ALK | anaplastic lymphoma kinase |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ECOG PS | Eastern Cooperative Oncology Group Performance Status |
| EGFR | epidermal growth factor receptor |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EQ-5D | European Quality of Life-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) |
| NSCLC | non-small cell lung cancer |
| 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 |
| SGB | Sozialgesetzbuch (Social Code Book) |
| 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. 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 10 February 2017.

### Research question

The aim of the present report was to assess the added benefit of pembrolizumab compared with the appropriate comparator therapy (ACT) as first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adult patients. The patients' tumours have to express programmed cell death ligand 1 (PD-L1) with a ≥ 50% tumour proportion score (TPS) (hereinafter referred to as TPS ≥ 50%). In addition, the tumours should not have activating epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations.

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

Table 2: Research question of the benefit assessment of pembrolizumab

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) without activating EGFR or ALK mutations in adults[b] | Patients with ECOG Performance Status 0, 1 or 2:<br>▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status<br>*or*<br>▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3])<br>*or*<br>▪ carboplatin in combination with nab-paclitaxel<br><br>Patients with ECOG Performance Status 2:<br>▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine |
| 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.<br>b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy.<br>ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TPS: Tumour Proportion Score; UICC: Union for International Cancer Control | |

The company principally followed the G-BA's specification of the ACT and chose a platinum-based combination chemotherapy (cisplatin or carboplatin in combination with a third-generation cytostatic agent) from the options presented. However, in its description of the research question, it did not address the fact that treatment with carboplatin-based combination chemotherapies is restricted to patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy. This restriction defined by the G-BA was considered in the present benefit assessment.

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

**Results**

***Study characteristics***

The KEYNOTE 024 study was used for the benefit assessment of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy. This was a randomized, open-label, active-controlled approval study on the comparison of pembrolizumab with a platinum-based combination chemotherapy.

The study included adult patients with histologically or cytologically confirmed metastatic NSCLC whose tumours express PD-L1 (strongly positive PD-L1 expression: TPS $\geq$ 50%). Patients were eligible if their tumours had no activating EGFR mutations or ALK translocations and they had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1. Previous systemic antineoplastic treatment for the metastatic stage was not allowed.

A total of 305 patients were randomly assigned to the study arms: 154 patients to the pembrolizumab arm and 151 patients to the comparator arm (platinum-based combination chemotherapy). Patients in the pembrolizumab arm received 200 mg pembrolizumab as 30-minute infusion every 3 weeks for a maximum of 35 cycles. The administration of pembrolizumab concurred with the requirements of the Summary of Product Characteristics (SPC). Patients in the comparator arm received 1 of 5 possible different platinum-based combination chemotherapies (cisplatin in combination with gemcitabine or pemetrexed or carboplatin in combination with gemcitabine or pemetrexed or paclitaxel) every 3 weeks for 4 to 6 cycles.

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

The patients were treated until disease progression, unacceptable side effects, or study discontinuation due to decision by the physician or the patient. Treatment was generally restricted by the maximum number of allowed cycles. Following discontinuation of the study

medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. There was no limitation regarding subsequent therapy. Switching from the comparator to the intervention group was allowed in case of disease progression and suitability.

***Relevant subpopulation of the study***

According to Appendix K of the Pharmaceutical Directive, prescription of carboplatin is restricted to patients with an increased risk of cisplatin-induced side effects (e.g. existing neuropathy or relevant hearing impairment, susceptibility to nausea, renal insufficiency or cardiac failure). Treatment with carboplatin-based chemotherapies in the KEYNOTE 024 study was not explicitly restricted according to these criteria. However, the investigator had to determine suitability of a patient for a specific platinum-based combination chemotherapy regimen and the respective dose at the start of the study before randomization. It was therefore possible to use a subpopulation of the KEYNOTE 024 study that contained patients treated in compliance with the Pharmaceutical Directive for the benefit assessment of pembrolizumab.

The company addressed the question whether treatment of patients with carboplatin in the KEYNOTE 024 study was in compliance with the criteria of the Pharmaceutical Directive by presenting the results of a retrospective interview for reasons of the decision for treatment with a carboplatin-based combination chemotherapy. The subpopulation relevant for the present benefit assessment (109 patients in the pembrolizumab arm and 107 patients in the comparator arm) contained the following patients:

- patients whom the investigator deemed suitable for cisplatin-based treatment and who were therefore to receive cisplatin-based treatment
- patients whom the investigator deemed unsuitable for cisplatin-based treatment and who were therefore to receive carboplatin-based treatment
- patients 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

It is assumed that the patients in the subpopulation who received carboplatin-based treatment fulfilled the criteria of the Pharmaceutical Directive for off-label use of carboplatin in the present therapeutic indication. An uncertainty remains whether the relevant subpopulation completely fulfilled the G-BA's specification of the ACT because the dossier contained no further details on the conduct of the interview.

***Risk of bias***

The risk of bias at study level was rated as low for the KEYNOTE 024 study. At outcome level, the risk of bias was rated as low for overall survival and as high for all other outcomes.

***Results***

*Mortality*

A statistically significant difference in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy.

*Morbidity*

- Symptoms

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13). The time to deterioration was considered in each case. Statistically significant differences in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy were shown for each of the following outcomes: dyspnoea, appetite loss, nausea and vomiting, constipation, alopecia, dysphagia, sore mouth and peripheral neuropathy. This resulted in a hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for these 8 outcomes.

A statistically significant difference in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for the outcomes "fatigue", "insomnia" and "haemoptysis"; the extent of the effect in these non-serious/non-severe outcomes was no more than marginal, however. No statistically significant differences between the treatment groups were shown for any further symptom outcomes. Hence there was no hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for any further symptom outcome; an added benefit is therefore not proven for any further symptom outcome.

- Health status

The outcome "health status" was recorded with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS). No statistically significant difference between the treatment groups was shown for the time to deterioration for the responder criterion of 7 points. For the responder criterion of 10 points, a statistically significant difference in favour of pembrolizumab versus cisplatin- or carboplatin-based chemotherapy was shown; the extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. Hence overall, there was no hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for the outcome "health status"; an added benefit is therefore not proven.

*Health-related quality of life*

Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC-QLQ-C30. The time to deterioration was considered. A statistically significant difference in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for the outcomes "physical functioning", "role functioning" and "social functioning". This resulted in a hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for these components of health-related quality of life.

No statistically significant difference between the treatment arms was shown for each of the outcomes "global health status", "emotional functioning" and "cognitive functioning". Hence there was no hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for these 3 outcomes; an added benefit for these 3 outcomes is therefore not proven.

*Side effects*

- Serious adverse events, discontinuation due to adverse events

There were no statistically significant differences between the treatment groups for the outcomes "serious adverse events (SAEs)" and "discontinuation due to AEs". Hence for these outcomes, there was no hint of greater or lesser harm from pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy; greater or lesser harm for these outcomes is therefore not proven.

- Severe adverse events (CTCAE grade ≥ 3)

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

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

    The dossier contained no usable data for the relevant subpopulation for the outcomes "immune-related AEs", "SAEs" and "severe AEs" (CTCAE grade ≥ 3). The results for the total population showed an effect to the disadvantage of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for all 3 outcomes on immune-related side effects.

- Further specific adverse events

  The dossier contained no data for the relevant subpopulation for the choice of further specific AEs. The results for the total population showed effects in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for gastrointestinal disorders, metabolism and nutrition disorders, nervous system disorders and blood and lymphatic system disorders (CTCAE grade ≥ 3). An effect to the disadvantage of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for skin and subcutaneous tissue disorders and respiratory, thoracic and mediastinal disorders (SAEs).

**Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]**

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

In the overall consideration, on the positive side, there is an indication of an added benefit with the extent "considerable" in the category "mortality". In addition, there were further hints of an added benefit in the categories "morbidity", "health-related quality of life" and in the category "side effects" for the outcome "severe AEs" (CTCAE grade ≥ 3). No usable data for the relevant subpopulation were available for immune-related side effects and specific AEs. The results of the total population showed a disadvantage of pembrolizumab for immune-related side effects and individual specific AEs. The effects of immune-related side effects and specific AEs in the relevant subpopulation were unclear. It was not assumed, however, that these completely outweighed the positive effects of pembrolizumab in severe AEs (CTCAE grade ≥ 3). Overall, a hint of lesser harm was assumed for the category "side effects" for the relevant subpopulation.

Since there were no subgroup analyses for the relevant subpopulation, there was an uncertainty whether effect modifications also existed in this population. For the total population, an indication of an effect modification for the characteristic "sex" was shown for overall survival and proof of an effect modification by the characteristic "sex" for 3 further outcomes. In the total population, this would lead to a separate derivation of the added benefit for men and women. Since the role of the effect modification by the characteristic "sex" in the relevant subpopulation remained unclear and there were additional principal uncertainties

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

regarding the choice of the relevant subpopulation, the certainty of conclusions on the basis of available data was limited.

In summary, there is a hint of a considerable added benefit of pembrolizumab in comparison with the ACT cisplatin- or carboplatin-based chemotherapy for patients with first-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS $\geq$ 50%) without activating EGFR or ALK mutations.

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

Table 3: Pembrolizumab – extent and probability of added benefit

| **Therapeutic indication** | **ACT**[a] | **Extent and probability of added benefit** |
|---|---|---|
| First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS $\geq$ 50%) without activating EGFR or ALK mutations in adults[b] | Patients with ECOG Performance Status 0, 1 or 2:<br>▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status<br>*or*<br>▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3])<br>*or*<br>▪ carboplatin in combination with nab-paclitaxel<br><br>**Patients with ECOG Performance Status 2:**<br>▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine | Hint of considerable added benefit |

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TPS: Tumour Proportion Score; UICC: Union for International Cancer Control

The approach for deriving an overall conclusion on 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 compared with the ACT as first-line treatment of metastatic NSCLC in adult patients. The patients' tumours have to express PD-L1 with a TPS ≥ 50%. In addition, the tumours should not have activating EGFR or ALK mutations.

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

Table 4: Research question of the benefit assessment of pembrolizumab

| **Therapeutic indication** | **ACT**[a] |
|---|---|
| First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) without activating EGFR or ALK mutations in adults[b] | Patients with ECOG Performance Status 0, 1 or 2:<br>▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status<br>*or*<br>▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3])<br>*or*<br>▪ carboplatin in combination with nab-paclitaxel<br><br>Patients with ECOG Performance Status 2:<br>▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine |
| 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.<br>b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy.<br>ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TPS: Tumour Proportion Score; UICC: Union for International Cancer Control | |

The company principally followed the G-BA's specification of the ACT and chose a platinum-based combination chemotherapy (cisplatin or carboplatin in combination with a third-generation cytostatic agent) from the options presented. However, in its description of the research question, it did not address the fact that treatment with carboplatin-based combination chemotherapies is restricted to patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy (see also Section 2.7.1 of the full dossier assessment). This restriction defined by the G-BA was considered in the present benefit assessment.

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

## 2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on pembrolizumab (status: 19 December 2016)
- bibliographical literature search on pembrolizumab (last search on 3 January 2017)
- search in trial registries for studies on pembrolizumab (last search on 3 January 2017)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 22 February 2017)

No additional relevant study was identified from the check.

### 2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy

| Study | Study category | | |
|---|---|---|---|
| | Study for approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) |
| KEYNOTE 024 | Yes | Yes | No |
| a: Study for which the company was sponsor.<br>RCT: randomized controlled trial; vs.: versus | | | |

The KEYNOTE 024 study was used for the benefit assessment of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy. This corresponded to the company's approach.

Section 2.6 contains a reference list for the study included.

### 2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| KEYNOTE 024 | RCT; open-label, parallel, crossover[b] | Adult patients (≥ 18 years) with histologically or cytologically confirmed stage IV NSCLC, PD-L1 expressing tumours (TPS ≥ 50%) without EGFR mutations or ALK translocations, ECOG ≤ 1, no previous systemic therapy[c] | Pembrolizumab (N = 154)<br>platinum-based chemotherapy[d] (N = 151)<br><br>Relevant subpopulation thereof[e]:<br>pembrolizumab (n = 109)<br>platinum-based chemotherapy (n = 107) | Screening: 30 days prior to the start of treatment<br>Treatment: until progression, unacceptable side effects, study discontinuation due to decision by the physician or the patient, complete response[f] or maximum number of allowed cycles[g]<br>Follow-up: outcome-specific, 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<br>9/2014–5/2016[h] | Primary: PFS<br>Secondary: overall survival, morbidity, health-related quality of life, AEs |

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Patients in the comparator arm could switch to the pembrolizumab arm in case of disease progression and suitability.
c: Patients with prior neoadjuvant or adjuvant treatment had to have received their last treatment at least 6 months before diagnosis of the metastatic disease.
d: Before randomization, chemotherapy was chosen for the individual patient from the following platinum-based combination chemotherapies and the corresponding dosages: cisplatin + gemcitabine, cisplatin + pemetrexed, carboplatin + gemcitabine, carboplatin + pemetrexed, carboplatin + paclitaxel. Patients with non-squamous histology could additionally receive maintenance treatment with pemetrexed after completion of at least 4 cycles with a platinum-based combination chemotherapy with pemetrexed or carboplatin + paclitaxel.
e: The relevant subpopulation excluded patients who, according to the results from the company's TPC interviews, were not treated according to the criteria of the Pharmaceutical Directive for off-label use of carboplatin.
f: In case of confirmed complete response (or in case of partial response or stable disease after the maximum number of cycles), patients in the pembrolizumab arm were allowed to temporarily discontinue treatment and reinitiate pembrolizumab treatment after subsequent confirmed progression ("second course phase"). Based on the study documents it can be assumed that only 1 patient reached the "second course phase".
g: The maximum treatment duration with pembrolizumab was 35 cycles; no patient reached this number of cycles. No maximum treatment duration for platinum-based combination chemotherapies can be inferred from the respective SPCs. 4 to at most 6 cycles of the respective therapy were administered in the study.
h: 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 after reaching 175 events for the outcome "PFS". All patients in the comparator arm were offered to switch to the pembrolizumab arm.

AE: adverse event; ALK: anaplastic lymphoma kinase; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; 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; RECIST: Response Evaluation Criteria in Solid Tumours; SPC: Summary of Product Characteristics; TPC: treatment of physician's choice; TPS: Tumour Proportion Score; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy

| Study | Intervention | Comparison |
|---|---|---|
| KEYNOTE 024 | Pembrolizumab 200 mg IV (infusion administered over 30 minutes) every 3 weeks<br><br>no change in dosing allowed (according to the SPC) | Platinum-based<br>combination chemotherapy[a] for 4 to 6 cycles:<br>▪ cisplatin 75 mg/m$^2$ IV (infusion administered over 6 to 8 hours) every 3 weeks<br>+<br>▫ pemetrexed 500 mg/m² IV (infusion administered over 10 minutes) every 3 weeks<br>or<br>▫ gemcitabine 1250 mg/m² IV (infusion administered over 30 minutes) on day 1 and 8 of a 3-week cycle<br>▪ carboplatin 5 or 6 mg/mL/min IV (AUC-dependent, infusion administered over 30 to 60 minutes) every 3 weeks<br>+<br>▫ pemetrexed 500 mg/m² IV (infusion administered over 10 minutes) every 3 weeks<br>or<br>▫ paclitaxel 200 mg/m² IV (infusion administered over 2 hours) every 3 weeks[b]<br>or<br>▫ gemcitabine 1250 mg/m² IV (infusion administered over 30 minutes) on day 1 and 8 of a 3-week cycle<br><br>▪ Administration according to the SPC |
| | **Pretreatment:**<br>▪ 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<br>**Non-permitted pretreatment:**<br>▪ systemic therapy for stage IV NSCLC<br>**Concomitant treatment:**<br>▪ drugs necessary for the patient's wellbeing<br>**Restricted concomitant treatment:**<br>▪ radiotherapy of individual lesions if these were no target lesion defined according to RECIST and radiotherapy was not aimed at tumour control<br>**Non-permitted concomitant treatment:**<br>▪ immunotherapies other than pembrolizumab<br>▪ other chemotherapies<br>▪ surgery for symptom and tumour control<br>▪ live vaccines<br>▪ corticosteroids except for the treatment of AEs or used as premedication of a platinum-based combination chemotherapy used in the study<br>▪ bisphosphonate or anti-RANK-L inhibitors | |

(continued)

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (continued)

a: Carboplatin + pemetrexed and cisplatin + pemetrexed were only allowed for patients with squamous cell histology (according to the SPC). Patients with non-squamous histology could additionally receive maintenance treatment with pemetrexed after completion of at least 4 cycles with a platinum-based combination chemotherapy with pemetrexed or carboplatin + paclitaxel.
b: The Pharmaceutical Directive on off-label use of carboplatin [3] allows paclitaxel as combination partner without mentioning the specified dosage.
AE: adverse event; AUC: area under the curve; EGFR: epidermal growth factor receptor; IV: intravenous; NSCLC: non-small cell lung cancer; RANK-L: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours; SPC: Summary of Product Characteristics; vs.: versus

The KEYNOTE 024 study was a randomized, open-label, controlled study.

The study included adult patients with histologically or cytologically confirmed metastatic NSCLC whose tumours express PD-L1 (strongly positive PD-L1 expression: TPS $\geq$ 50%). Patients were eligible if their tumours had no activating EGFR mutations or ALK translocations and they had an ECOG PS of 0 or 1. Previous systemic antineoplastic treatment for the metastatic stage was not allowed.

In the KEYNOTE 024 study, the PD-L1 status of the tumour tissue was determined using immunohistochemistry in formalin-fixed tumour samples, which were obtained either at the time point of diagnosis or after diagnosis of the metastatic disease. Samples from biopsies obtained before neoadjuvant or adjuvant treatment were not permitted to be used for this assessment. PD-L1 expression was assessed with the Dako Commercial Ready Assay (monoclonal, PD-L1-targeted, antibody of the 22C3 clone). The percentage of cells presenting a positive membrane staining for PD-L1 was determined with a minimum of 100 cells.

According to the company, the exclusion of patients with activating EGFR mutations or ALK translocations in the tumour referred to mutations that have to be demonstrated for eligibility to treatment with the tyrosine kinase inhibitors erlotinib, gefitinib or afatinib. Evidence of testing for these mutations had to be presented for all patients with non-squamous histology and for patients for whom the test was clinically recommended. Details on the testing were not provided.

The population investigated in the KEYNOTE 024 study corresponded to the therapeutic indication of pembrolizumab in the present research question.

Randomization was stratified by histology (squamous, non-squamous), geographical region (East Asia, not East Asia) and ECOG PS (0, 1). A total of 305 patients were randomly assigned to the study arms: 154 patients to the pembrolizumab arm and 151 patients to the comparator arm (platinum-based combination chemotherapy).

Patients in the pembrolizumab arm received 200 mg pembrolizumab as 30-minute infusion every 3 weeks. The administration of pembrolizumab concurred with the requirements of the SPC [4]. The maximum treatment duration for pembrolizumab was 35 cycles. Patients in the comparator arm received 1 of 5 possible different platinum-based combination chemotherapies for 4 to 6 cycles every 3 weeks. At the start of the study, before randomization, the investigator decided which specific combination chemotherapy the individual patient would receive. After the chemotherapy (only if there was no progression), patients with non-squamous histology were strongly recommended maintenance treatment with pemetrexed. 46 (37%) of the patients with non-squamous histology in the comparator arm received such maintenance treatment.

The platinum-based combination chemotherapies were administered without relevant deviation from the approvals [5-8]. Neither the SPC [9] nor the Pharmaceutical Directive on off-label use [3] contains information on the dosage of paclitaxel in combination with carboplatin. In the KEYNOTE 024 study, paclitaxel was administered at a dosage of 200 mg/m$^2$ body surface area. In both study arms, prior and concomitant treatments were also administered in accordance with the approvals.

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

The patients were treated until disease progression, unacceptable side effects, or study discontinuation due to decision by the physician or the patient. In principle, treatment was restricted by the maximum number of allowed cycles, which was reached by no patient in the pembrolizumab arm and by 29 (19.3%) patients in the comparator arm.

Following discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could be treated with subsequent therapies. There was no limitation regarding subsequent therapy. Switching treatment from the comparator to the experimental intervention was allowed in case of disease progression and suitability. A total of 66 (43.7%) patients had switched from the comparator arm to the pembrolizumab arm during the study until the time point of the second interim analysis. The proportion of patients with subsequent therapy was 16.6% in the comparator arm (in addition to the patients who switched treatment to the pembrolizumab arm) and 22.7% in the pembrolizumab arm. The company's dossier contained no details on the subsequent therapies. This information would have been necessary in the dossier for a description of the therapeutic strategies used in the respective arm, however.

**Implementation of the appropriate comparator therapy in the KEYNOTE 024 study**

In the comparator arm of the KEYNOTE 024 study (N = 151), 68% (N = 103) of the patients were treated with a carboplatin-based combination chemotherapy and 31% (N = 47) with a cisplatin-based combination chemotherapy. The distribution of the 5 possible combination

chemotherapies in the total population is presented in Table 20 of the full dossier assessment. No information on this was available for the subpopulation.

According to Appendix K of the Pharmaceutical Directive, prescription of carboplatin is restricted to patients with an increased risk of cisplatin-induced side effects (e.g. existing neuropathy or relevant hearing impairment, susceptibility to nausea, renal insufficiency or cardiac failure). Patients who are eligible for approved treatments should not be treated with a carboplatin-based chemotherapy [3]. Treatment with carboplatin-based chemotherapies in the KEYNOTE 024 study was not explicitly restricted according to these criteria. However, the investigator had to determine suitability of a patient for a specific platinum-based combination chemotherapy regimen and the respective dose at the start of the study before randomization. Patients who had received platinum-based treatment in the neoadjuvant or adjuvant setting were not permitted to receive retreatment with the same combination chemotherapy in the comparator arm unless they had a known contraindication to the adjuvant treatment option.

The company addressed the question whether treatment of patients with carboplatin in the KEYNOTE 024 study was in compliance with the criteria of the Pharmaceutical Directive by presenting the results of a retrospective interview for reasons of the decision for treatment with a carboplatin-based combination chemotherapy in Module 4 A (referred to by the company as “treatment of physician’s choice [TPC] interview”). This retrospective interview was only conducted for patients allocated to carboplatin-based chemotherapy by the investigator before randomization (N = 202). Results of the TPC interview were available for 199 (98.5%) of these 202 patients. According to the retrospective interview, the investigators had considered 74 (37.2%) of these patients unsuitable for chemotherapy with cisplatin at the start of the study (see Table 8). 125 (62.8%) of the patients were principally suitable for a combination chemotherapy with cisplatin. In these patients, the decision to still use a carboplatin-containing chemotherapy was based on other reasons (benefit-risk profile in favour of carboplatin, carboplatin was the standard therapy in the practice and other reasons). The following table shows the interview results in detail.

Table 8: Results of the company's interviews on the treatment rationale of carboplatin-based combination chemotherapies in the KEYNOTE 024 study (total population)

| **Answers in the TPC interviews on the treatment rationale of a carboplatin-based combination chemotherapy in the KEYNOTE 024 study** | **Randomized patients N (%[a])** |
|---|---|
| Patients allocated to carboplatin-based combination chemotherapy before randomization | 202 |
| Patients for whom results of the interview are available[b] | 199 |
| Considered suitable by the investigator for cisplatin-based combination chemotherapy | 125 (62.8) |
| Reasons why the patient should receive carboplatin-based combination chemotherapy in the study despite suitability for cisplatin: | |
| ▫ Benefit-risk profile in favour of carboplatin | 41 (32.8) |
| ▫ Carboplatin is standard therapy in the practice | 82 (65.6) |
| ▫ Other reasons[c] | 24 (19.2) |
| Considered unsuitable by the investigator for cisplatin-based combination chemotherapy[d] | 74 (37.2) |

a: According to the company, choosing several reasons for a treatment rationale was possible in the interview; percentages therefore add up to over 100%.
b: The TPC interviews were conducted retrospectively for the KEYNOTE 024 study; according to the company, no information on the treatment rationale could be determined for 3 patients. The response rate is 98.5%.
c: According to the company, other reasons in the interview included patient preference, shorter administration duration of carboplatin or older patient, for example.
d: According to the company, the reasons stated for the patients' unsuitability for a cisplatin-based combination chemotherapy included cardiac failure, renal insufficiency, hearing impairment or susceptibility to nausea and vomiting. According to the company, the reasons stated were in compliance with the contraindications described in the SPC of cisplatin, the information provided in the Pharmaceutical Directive on off-label use of carboplatin-based combination chemotherapies in NSCLC and the recommendations of the current guidelines on the first-line treatment of NSCLC [3,7,10,11].
NSCLC: non-small cell lung cancer; SPC: Summary of Product Characteristics; TPC: treatment of physician's choice

The results of the interviews therefore showed that not all patients in the KEYNOTE 024 study were treated in compliance with the criteria of the Pharmaceutical Directive. Consequently, only a subpopulation of the study was relevant for the present benefit assessment.

**Relevant subpopulation of the study**

The decision which treatment the patients in the study were to receive in case of allocation to the comparator arm was to be made already before randomization. For this reason, it was possible to use a subpopulation of the KEYNOTE 024 study that contained patients treated in compliance with the Pharmaceutical Directive for the benefit assessment of pembrolizumab. Due to this study design, the randomization was maintained also for the subpopulation.

The company presented a subgroup analysis according to the treatment allocated by the investigator before randomization (and its justification) (treatment of investigator's choice under consideration of the TPC answers). The company distinguished between patients with approval-compliant or justified off-label treatment with chemotherapy and patients who

received carboplatin for other reasons (e.g. carboplatin is standard therapy in the practice or patient preference, shorter administration duration of carboplatin or older patient [see Table 8]). Both patients deemed unsuitable for cisplatin treatment by the investigator at the time point of randomization and patients who would have been suitable for treatment with cisplatin, but who received carboplatin due to the better benefit-risk profile, were considered by the company for the justified off-label use.

Hence the relevant subpopulation (109 patients in the pembrolizumab arm and 107 patients in the comparator arm) taken from this subgroup contained the following patients:

- patients whom the investigator deemed suitable for cisplatin-based treatment and who were therefore to receive cisplatin-based treatment
- patients whom the investigator deemed unsuitable for cisplatin-based treatment and who were therefore to receive carboplatin-based treatment
- patients 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

It is assumed that the patients in the subpopulation who received carboplatin-based treatment fulfilled the criteria of the Pharmaceutical Directive [3] for off-label use of carboplatin in the present therapeutic indication. An uncertainty remains whether the relevant subpopulation completely fulfilled the G-BA's specification of the ACT because the dossier contained no further details on the conduct of the interview.

**Planned duration of follow-up**

Table 9 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 9: Planned duration of follow-up – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up** |
|---|---|
| KEYNOTE 024 | |
| Mortality | |
| Overall survival | After the end of treatment (except due to progression): every 3 months until progression<br>After progression or initiation of a new antineoplastic treatment: every 2 months until death |
| Morbidity | |
| Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13) | At treatment weeks 0, 3 and 6 and then every 9 weeks, at end of treatment and 30 days after the last dose of the study medication<br>At the end of treatment before progression: every 9 weeks until progression or initiation of new antineoplastic treatment |
| Health status (EQ-5D VAS) | At treatment weeks 0, 3 and 6 and then every 9 weeks, at end of treatment and 30 days after the last dose of the study medication<br>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) | At treatment weeks 0, 3 and 6 and then every 9 weeks, at end of treatment and 30 days after the last dose of the study medication<br>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 is initiated, whichever occurred first) then: only recording of SAEs considered to be treatment-related |

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Only overall survival was recorded until the end of the study participation.

The observation periods for the outcomes “side effects”, “morbidity” and “health-related quality of life” were systematically shortened because they were only recorded for the time period of treatment (plus 30 days or 90 days for SAEs). 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**

The characteristics of the study population were only available for the total population of patients in the KEYNOTE 024 study and are presented in Appendix A (Table 21) of the full dossier assessment.

The mean age of the patients included in the KEYNOTE 024 study was 64 years. About 40% of the patients were women. About 80% of the patients were white; the proportion of Asian patients was approximately 15%. Two thirds of the patients had an ECOG PS of 1; the other patients of 0. Almost all patients had disease stage IV. Most patients had no brain metastases. The proportion of patients with treatment discontinuation was lower in the pembrolizumab arm than in the comparator arm; at the time point of the second interim analysis, 80 (51.9%) of the patients in the pembrolizumab arm and 106 (70.7%) of the patients in the comparator arm had discontinued the study treatment. The 2 most common reasons for treatment discontinuation were disease progression and AEs.

There was no information on these characteristics for the relevant subpopulation.

**Course of the study**

Information on the mean and median treatment duration of the patients was only available for the total population of patients in the KEYNOTE 024 study and is presented in Appendix A (Table 22) of the full dossier assessment. There was no information for the relevant subpopulation.

The median treatment duration for the total population in the KEYNOTE 024 study was twice as high in the pembrolizumab arm (7.0 months) as in the comparator arm (3.5 months). The difference in treatment duration was caused by differences in the treatment discontinuation rates due to disease progression and AEs and in the different maximum treatment duration specified (pembrolizumab arm: 35 cycles, comparator arm: 4 to 6 cycles) (Table 22 of the full dossier assessment). Module 4 A contains discrepant information for the median treatment duration in the comparator arm in comparison with Module 5 (6.4 months instead of 3.5 months). Due to missing information in the dossier, there was also uncertainty whether the maintenance treatment with pemetrexed in the comparator arm was rated as treatment or whether reaching the maximum number of 4 to 6 cycles was recorded as end of treatment.

The dossier contained no information on observation periods of individual outcomes also for the total population. The differences in treatment and observation periods (except for the outcome “overall survival”) are presumably similar because the outcomes on morbidity, health-related quality of life and side effects (except SAEs) were each to be recorded until 30 days after the last administration of the study medication (or until progression in case of end of treatment before progression). Follow-up observation for SAEs was either 90 days or until 30 days after the last dose of the study medication if new antineoplastic treatment was initiated, whichever occurred first.

**Risk of bias at study level**

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Reporting independent of the results | No additional aspects | Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | Patient | Treating staff | | | |
| KEYNOTE 024 | Yes | Yes | No | No | Yes | Yes | Low |
| RCT: randomized controlled trial; vs.: versus | | | | | | | |

The risk of bias at study level was rated as low for the study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

## 2.4 Results on added benefit

### 2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - Overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-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 $\geq 3$)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes concurred with that of the company.

Table 11 shows for which outcomes data for the relevant subpopulation were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation)

| 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 |
| KEYNOTE 024 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No[a] | No[a] | No[a] | No[a] |

a: No data available for the relevant subpopulation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-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 Risk of bias

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation)

| 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-LC30) | SAEs | Discontinuation due to AEs | Severe AEs (CTCAE grade ≥ 3) | Immune-related AEs | Immune-related SAEs | Immune-related severe AEs (CTCAE grade ≥ 3) | Further specific AEs |
| KEYNOTE 024 | L | L | H[a, b, c] | H[a, b, c] | H[a, b, c] | H[b] | H[a] | H[b] | –[d] | –[d] | –[d] | –[d] |

a: Lack of blinding in subjective recording of outcomes.
b: High proportion of observations with potentially informative censoring.
c: Unclear proportion of missing values in the subpopulation.
d: No data available for the relevant subpopulation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome "overall survival" was rated as low in the relevant subpopulation. This concurs with the company's assessment (in relation to the total population), albeit with different justification (see Section 2.7.2.4.2 of the full dossier assessment).

Due to the lack of blinding in subjective recording of outcomes and the high proportion of observations with potentially informative censoring, the risk of bias for the outcomes on symptoms and quality of life in the relevant subpopulation was rated as high (see Section 2.7.2.4.2 of the full dossier assessment). In comparison with the total population, there was additional uncertainty regarding the proportion of missing values for the subpopulation. The company also rated the risk of bias in the total population for these outcomes as high.

For the outcomes on side effects (SAEs and severe CTCAE grade ≥ 3 AEs), the risk of bias for the relevant subpopulation is to be regarded as high due to the large proportions of observations with potentially informative censoring (see Section 2.7.2.4.2 of the full dossier assessment). The risk of bias was also high for the outcome "discontinuation due to AEs" due to the lack of blinding. Due to the potentially informative censoring, the company rated the risk of bias for these outcomes in the total population also as high.

No data for the relevant subpopulation were available for immune-related side effects and specific AEs. The risk of bias for these outcomes was therefore not assessed. This deviates from the approach of the company, which considered the risk of bias as high for these outcomes (regarding the total population) due to the potentially informative censoring.

### 2.4.3 Results

The results on the comparison of pembrolizumab with a cisplatin- or carboplatin-based chemotherapy in patients with first-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS $\geq$ 50%) are summarized in Table 13. The results for the relevant subpopulation were taken from the subgroup analyses of the characteristic "treatment at the investigator's discretion under consideration of the TPC answers" presented by the company in Module 4 A. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations. Kaplan-Meier curves on the outcomes included were not available for the relevant subpopulation.

The results for the total population are presented as additional information in Appendix A and Appendix B of the full dossier assessment.

Table 13: Results (overall survival, morbidity, health-related quality of life and side effects) – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation)

| **Study**<br>**Outcome category**<br>**Outcome** | **Pembrolizumab** | | **Cisplatin- or carboplatin-based chemotherapy[a]** | | **Pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy** |
|---|---|---|---|---|---|
| | **N** | **Median survival time in months [95% CI]**<br>**Patients with event n (%)** | **N** | **Median survival time in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]; p-value[b]** |
| **KEYNOTE 024** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 109 | NA [NC; NC]<br>30 (27.5) | 107 | 12.6 [9.4; NC]<br>44 (41.1) | 0.57 [0.36; 0.92];<br>0.020 |
| **Morbidity** | | | | | |
| Symptoms (EORTC QLQ-C30 symptom scales) – time to deterioration[c] | | | | | |
| Dyspnoea | 107 | NA [9.9; NC]<br>28 (26.2) | 105 | 6.2 [4.2; NC]<br>41 (39.0) | 0.54 [0.33; 0.87];<br>0.012 |
| Fatigue | 107 | 3.5 [1.4; 9.6]<br>53 (49.5) | 105 | 2.4 [1.4; 3.5]<br>64 (61.0) | 0.69 [0.47; 1.00];<br>0.049 |
| Insomnia | 107 | NA [NC; NC]<br>28 (26.2) | 105 | 6.5 [4.2; NC]<br>40 (38.1) | 0.58 [0.35; 0.94];<br>0.028 |
| Pain | 107 | 7.6 [3.5; 11.8]<br>49 (45.8) | 105 | 4.5 [3.4; 6.4]<br>53 (50.5) | 0.68 [0.46; 1.03];<br>0.067 |
| Appetite loss | 107 | NA [NC; NC]<br>30 (28.0) | 105 | 4.6 [3.5; 9.9]<br>45 (42.9) | 0.50 [0.31; 0.81];<br>0.004 |
| Diarrhoea | 107 | NA [12.5; NC]<br>23 (21.5) | 105 | NA [7.1; NC]<br>29 (27.6) | 0.60 [0.34; 1.05];<br>0.073 |
| Nausea and vomiting | 107 | 15.9 [15.9; NC]<br>28 (26.2) | 105 | 4.9 [1.5; 7.2]<br>46 (43.8) | 0.38 [0.24; 0.62];<br>< 0.001 |
| Constipation | 107 | NA [7.6; NC]<br>33 (30.8) | 105 | 4.4 [1.4; 8.3]<br>47 (44.8) | 0.50 [0.32; 0.79];<br>0.003 |
| Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[c] | | | | | |
| Dyspnoea | 107 | 9.7 [3.4; NC]<br>45 (42.1) | 105 | 4.0 [2.2; 5.6]<br>49 (46.7) | 0.83 [0.55; 1.26];<br>0.381 |
| Pain (chest) | 107 | NA [NC; NC]<br>20 (18.7) | 105 | NA [7.1; NC]<br>28 (26.7) | 0.60 [0.33; 1.07];<br>0.084 |
| Pain (arm/shoulder) | 107 | 11.8 [11.8; NC]<br>31 (29.0) | 105 | 8.3 [7.8; NC]<br>28 (26.7) | 0.82 [0.48; 1.39];<br>0.459 |
| Pain (other) | 107 | 7.6 [5.1; 12.6]<br>45 (42.1) | 105 | 6.1 [3.4; 8.3]<br>46 (43.8) | 0.72 [0.47; 1.10];<br>0.126 |
| Cough | 107 | NA [8.5; NC]<br>30 (28.0) | 105 | 8.2 [5.8; 12.2]<br>35 (33.3) | 0.64 [0.38; 1.06];<br>0.085 |

(continued)

Table 13: Results (overall survival, morbidity, health-related quality of life and side effects) – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation) (continued)

| Study<br>Outcome category<br>Outcome | Pembrolizumab | | Cisplatin- or carboplatin-based chemotherapy[a] | | Pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy |
|---|---|---|---|---|---|
| | N | Median survival time in months [95% CI]<br>Patients with event n (%) | N | Median survival time in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[b] |
| Symptoms (EORTC QLQ-LC13 symptom scales) – time to deterioration[c] | | | | | |
| Haemoptysis | 107 | NA [NC; NC]<br>7 (6.5) | 105 | NA [NC; NC]<br>13 (12.4) | 0.38 [0.15; 0.97];<br>0.042 |
| Alopecia | 107 | NA [NC; NC]<br>9 (8.4) | 148 | 3.4 [1.9; 5.8]<br>50 (47.6) | 0.09 [0.04; 0.19];<br>< 0.001 |
| Dysphagia | 107 | NA [NC; NC]<br>18 (16.8) | 105 | 12.2 [6.5; NC]<br>31 (29.5) | 0.42 [0.23; 0.76];<br>0.004 |
| Sore mouth | 107 | NA [NC; NC]<br>19 (17.8) | 105 | 7.2 [4.9; NC]<br>36 (34.3) | 0.31 [0.17; 0.55];<br>< 0.001 |
| Peripheral neuropathy | 107 | 13.8 [10.0; NC]<br>29 (27.1) | 105 | 5.7 [3.9; 7.4]<br>45 (42.9) | 0.47 [0.29; 0.75];<br>0.002 |
| Health status (EQ-5D VAS) – time to deterioration | | | | | |
| Responder criterion 10 points | 107 | 9.7 [3.5; NC]<br>42 (39.3) | 105 | 3.7 [1.4; 4.8]<br>56 (53.3) | 0.61 [0.40; 0.92];<br>0.018 |
| Responder criterion 7 points | 107 | 3.6 [1.4; NC]<br>50 (46.7) | 105 | 1.9 [1.4; 3.7]<br>61 (58.1) | 0.68 [0.46; 1.01];<br>0.055 |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30 functional scales – time to deterioration[c] | | | | | |
| Global health status | 107 | 7.8 [3.4; NC]<br>45 (42.1) | 105 | 3.0 [1.8; 4.2]<br>52 (49.5) | 0.69 [0.46; 1.04];<br>0.079 |
| Emotional functioning | 107 | NA [11.8; NC]<br>28 (26.2) | 105 | 10.7 [5.5; NC]<br>35 (33.3) | 0.60 [0.36; 1.00];<br>0.052 |
| Cognitive functioning | 107 | 15.4 [5.5; NC]<br>42 (39.3) | 105 | 4.6 [2.8; NC]<br>45 (42.9) | 0.71 [0.47; 1.10];<br>0.123 |
| Physical functioning | 107 | 8.5 [3.5; NC]<br>47 (43.9) | 105 | 1.8 [1.4; 3.7]<br>62 (59.0) | 0.48 [0.32; 0.71];<br>< 0.001 |
| Role functioning | 107 | NA [3.5; NC]<br>40 (37.4) | 105 | 4.0 [1.9; 6.1]<br>54 (51.4) | 0.56 [0.37; 0.85];<br>0.006 |
| Social functioning | 107 | NA [7.6; NC]<br>36 (33.6) | 105 | 2.2 [1.4; 4.0]<br>56 (53.3) | 0.42 [0.27; 0.64];<br>< 0.001 |

(continued)

Table 13: Results (overall survival, morbidity, health-related quality of life and side effects) – RCT, direct comparison: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation) (continued)

| **Study**<br>**Outcome category**<br>**Outcome** | **Pembrolizumab** | | **Cisplatin- or carboplatin-based chemotherapy[a]** | | **Pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy** |
|---|---|---|---|---|---|
| | **N** | **Median survival time in months [95% CI]**<br>**Patients with event n (%)** | **N** | **Median survival time in months [95% CI]**<br>**Patients with event n (%)** | **HR [95% CI]; p-value[b]** |
| **Side effects** | | | | | |
| AEs (supplementary information) | 109 | 0.2 [0.1; 0.4]<br>104 (95.4) | 106 | 0.1 [0.1; 0.2]<br>102 (96.2) | – |
| SAEs | 109 | 12.4 [6.2; NC]<br>47 (43.1) | 106 | NA [3.7; NC]<br>49 (46.2) | 0.87 [0.58; 1.30]; 0.503 |
| Severe AEs (CTCAE grade ≥ 3) | 109 | 7.6 [4.2; NC]<br>56 (51.4) | 106 | 1.4 [1.1; 2.1]<br>75 (70.8) | 0.49 [0.34; 0.70]; < 0.001 |
| Specific AEs | | | | | |
| Immune-related AEs | No data available for the relevant subpopulation | | | | |
| Immune-related SAEs | No data available for the relevant subpopulation | | | | |
| Immune-related severe AEs (CTCAE grade ≥ 3) | No data available for the relevant subpopulation | | | | |
| Further specific AEs | No data available for the relevant subpopulation | | | | |
| | **N** | **Patients with event n (%)** | **N** | **Patients with event n (%)** | **RR [95% CI]; p-value[d]** |
| Discontinuation due to AEs | 109 | 12 (11.0) | 106 | 19 (17.9) | 0.61 [0.31; 1.20]; 0.154 |

a: Before randomization, chemotherapy was chosen for the individual patient from the following combination chemotherapies: cisplatin + gemcitabine, cisplatin + pemetrexed, carboplatin + gemcitabine, carboplatin + pemetrexed, carboplatin + paclitaxel.
b: Effect, CI and p-value: Cox proportional hazards model stratified by geographical region (East Asia vs. not East Asia), ECOG Performance Status (0 vs. 1) and histology (squamous vs. non-squamous), p-value and Wald test.
c: The time to deterioration by at least 10 points is provided.
d: Institute‘s calculation of RR, CI (asymptotic) and p-value (unconditional exact test [CSZ method according to [12]]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

From the available data, at most indications, e.g. of an added benefit, can be derived for overall survival, and at most hints for all other outcomes due to the high risk of bias.

The company assessed the added benefit of pembrolizumab on the basis of the total population of the KEYNOTE 024 study without considering that, for some of the patients treated with a carboplatin-based combination chemotherapy, this treatment did not comply with the criteria of the Pharmaceutical Directive (see also Section 2.3.2). In Module 4 A, the company presented results for the relevant subpopulation of the present research question in form of subgroup analyses, but derived no added benefit for this subpopulation from them. The extent of the deviation between the assessment of the outcomes in the present benefit assessment (on the basis of the relevant subpopulation) and the company's assessment is described in summary form in the end of this section.

**Mortality**

***Overall survival***

A statistically significant difference in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy.

**Morbidity**

***Symptoms***

Outcomes of symptoms were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-LC13. The time to deterioration by at least 10 points was considered. Below, first the symptom outcomes with statistically significant group differences are described.

*Dyspnoea, appetite loss, nausea and vomiting, constipation, alopecia, dysphagia, sore mouth, peripheral neuropathy*

Statistically significant differences in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy were shown for each of the following outcomes: dyspnoea, appetite loss, nausea and vomiting, constipation, alopecia, dysphagia, sore mouth and peripheral neuropathy. This resulted in a hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for these 8 outcomes.

*Further outcomes on symptoms*

A statistically significant difference in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for the outcomes "fatigue", "insomnia" and "haemoptysis"; the extent of the effect in these non-serious/non-severe outcomes was no more than marginal, however. Hence overall, there was no hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for these 3 outcomes; an added benefit is therefore not proven. No statistically significant

differences between the treatment groups were shown for any further outcomes on symptoms. Hence there was no hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for any further symptom outcome; an added benefit is therefore not proven for any further symptom outcome.

***Health status***

The outcome "health status" was recorded with the EQ-5D VAS. No statistically significant difference between the treatment groups was shown for the time to deterioration for the responder criterion of 7 points. For the responder criterion of 10 points, a statistically significant difference in favour of pembrolizumab versus cisplatin- or carboplatin-based chemotherapy was shown; the extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. Hence overall, there was no hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for the outcome "health status"; an added benefit is therefore not proven.

**Health-related quality of life**

Health-related quality of life was recorded with the functional scales and with the scale for the recording of the global health status of the disease-specific instrument EORTC-QLQ-C30. The time to deterioration by at least 10 points was considered.

A statistically significant difference in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for the outcomes "physical functioning", "role functioning" and "social functioning". This resulted in a hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for these 3 components of the category "health-related quality of life".

No statistically significant difference between the treatment arms was shown for each of the outcomes "global health status", "emotional functioning" and "cognitive functioning". Hence there was no hint of an added benefit of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy for these outcomes; an added benefit for these 3 outcomes is therefore not proven.

**Side effects**

***Serious adverse events, discontinuation due to adverse events***

There were no statistically significant differences between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence for these outcomes, there was no hint of greater or lesser harm from pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy; greater or lesser harm for these outcomes is therefore not proven.

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

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

***Specific adverse events***

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

The dossier contained no usable data for the relevant subpopulation for the outcomes "immune-related AEs", "SAEs" and "severe AEs" (CTCAE grade ≥ 3) (see Section 2.7.2.4.3 of the full dossier assessment). The results for the total population are presented in Appendix A, Table 23, of the full dossier assessment. An effect to the disadvantage of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for all 3 outcomes on immune-related AEs.

*Further specific adverse events*

The dossier contained no data for the relevant subpopulation for the choice of further specific AEs (see Section 2.7.2.4.3 of the full dossier assessment). The results for the total population are presented in Appendix A, Table 23, of the full dossier assessment. Effects in favour of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy were shown for gastrointestinal disorders, metabolism and nutrition disorders, nervous system disorders and blood and lymphatic system disorders (CTCAE grade ≥ 3). An effect to the disadvantage of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy was shown for skin and subcutaneous tissue disorders and respiratory, thoracic and mediastinal disorders (SAEs).

**Comparison with the company's assessment of the results on the basis of the total population**

For most outcomes, the assessment of the added benefit concurred with that of the company. Only for the outcomes "fatigue" (EORTC QLQ-C30), "health status" (EQ-5D VAS, response criterion of 10 points) and "global health status" (EORTC QLQ-C30) did the company derive a hint of an added benefit of pembrolizumab in comparison with a platinum-based combination chemotherapy on the basis of the total population, whereas no proof of an added benefit for these outcomes has been found in the present benefit assessment.

The dossier contained no usable data for the relevant subpopulation for the outcomes "immune-related AEs", "immune-related SAEs" and "immune-related severe AEs" (CTCAE grade ≥ 3). The company derived a hint of greater harm of pembrolizumab in comparison with a platinum-based combination chemotherapy for the total population. The dossier contained no usable data for the choice of further specific AEs for the relevant subpopulation. For the total population, the company derived both several hints of greater harm and several

hints of an added benefit of pembrolizumab in comparison with a platinum-based combination chemotherapy.

### 2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present assessment:

- age (< 65 years, ≥ 65 years)
- sex (men, women)
- region (not East Asia, East Asia)
- smoking status (active, former, never)
- histology (squamous, non-squamous)
- brain metastases (yes, no)

The dossier contained no subgroup analyses for the relevant subpopulation, however. The results of the subgroup results presented by the company on the relevant subgroup characteristics are shown for the total population in Appendix A (Table 24) of the full dossier assessment. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. For the outcome "overall survival", results are presented if there was at least an indication of an interaction between treatment and subgroup characteristic. For all other outcomes, only results for which there was proof of an interaction are presented due to the different treatment durations and resulting different observation periods and the potentially informative censoring (see Section 2.7.2.2 of the full dossier assessment). In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The company assessed the added benefit on the basis of the total population. For the total population, the company considered no subgroup results for any of the outcomes used by the company for the outcome-specific derivation of the added benefit. In Module 4 A (Section 4.3.1.3.2.1) of the dossier, the company described that neither indications nor proof of effect modifications were shown in the subgroup analyses for overall survival, although there was an indication (p = 0.089) of an effect modification for the characteristic "sex" for this outcome. In the subgroups, an advantage for overall survival was shown for men, but not for women. In addition, there was proof of an effect modification by the characteristic "sex" for 3 further outcomes (nausea and vomiting, pain [chest] and emotional functioning). In each case, an effect was observed in men, but not in women.

## 2.5 Extent and probability of added benefit

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

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

### 2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in the following assessments for pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy in patients with first-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS ≥ 50%):

- an indication of an added benefit for the outcome "overall survival"
- a hint of an added benefit for each of the following outcomes: dyspnoea, appetite loss, nausea and vomiting, constipation, alopecia, dysphagia, sore mouth, peripheral neuropathy, physical functioning, role functioning and social functioning
- a hint of lesser harm for the outcome "severe AEs" (CTCAE grade ≥ 3)

No data for the subpopulation were available for immune-related AEs, for which greater harm was shown in the total population. There were also no data for the subpopulation for specific AEs, for which both positive and negative effects of pembrolizumab were shown in the total population.

**Determination of the outcome category for the outcomes "symptoms" and "health status"**

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

The assessment regarding the outcome category of the EORTC QLQ-C30 and EORTC QLQ-LC13 symptom scales, which showed an added benefit, depends on the severity of the respective symptom. The results on common AEs recorded in the KEYNOTE 024 study were used by CTCAE grades to be able to assess the severity of these symptoms. These were only available for the total population (see Appendix C of the full dossier assessment). For the total study population, the corresponding AEs were mostly not severe (CTCAE grade 1 and 2), however. Correspondingly, the results of the symptoms were allocated to the outcome category "non-serious/non-severe symptoms/late complications". For the outcomes "dyspnoea", "sore mouth", "dysphagia" and "peripheral neuropathy", this allocation deviates from the assessment of the company (see Section 2.7.2.8.2 of the full dossier assessment).

The outcome "health status" was allocated to the outcome category of non-serious/non-severe symptoms/late complications because there was no proof of serious change for the patients included in the KEYNOTE 024 study.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 14).

Table 14: Extent of added benefit at outcome level: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation)

| **Outcome category**<br>**Outcome** | **Pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy[a]**<br>**Median time to event or proportion of events**<br>**Effect estimate [95% CI]; p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| **Mortality** | | |
| Overall survival | Median: NA vs. 12.6 months<br>HR: 0.57 [0.36; 0.92]; p = 0.020<br>probability: "indication" | Outcome category: mortality<br>$0.85 \leq CI_u < 0.95$<br>added benefit, extent: "considerable" |
| **Morbidity** | | |
| Symptoms | | |
| EORTC QLQ-C30 (symptom scales) – time to deterioration[d] | | |
| Dyspnoea | Median: NA vs. 6.2 months<br>HR: 0.54 [0.33; 0.87]; p = 0.012<br>probability: "hint" | Outcome category: non-serious/ non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>added benefit, extent: "minor" |
| Fatigue | Median: 3.5 vs. 2.4 months<br>HR: 0.69 [0.47; 1.00]; p = 0.049 | Outcome category: non-serious/ non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>Lesser benefit/added benefit not proven[e] |
| Insomnia | Median: NA vs. 6.5 months<br>HR: 0.58 [0.35; 0.94]; p = 0.028 | Outcome category: non-serious/ non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>Lesser benefit/added benefit not proven[e] |
| Pain | Median: 7.6 vs. 4.5 months<br>HR: 0.68 [0.46; 1.03]; p = 0.067 | Lesser benefit/added benefit not proven |
| Appetite loss | Median: NA vs. 4.6 months<br>HR: 0.50 [0.31; 0.81]; p = 0.004<br>probability: "hint" | Outcome category: non-serious/ non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>added benefit, extent: "minor" |
| Diarrhoea | Median: NA vs. NA months<br>HR: 0.60 [0.34; 1.05]; p = 0.073 | Lesser benefit/added benefit not proven |
| Nausea and vomiting | Median: 15.9 vs. 4.9 months<br>HR: 0.38 [0.24; 0.62]; p < 0.001<br>probability: "hint" | Outcome category "non-serious/non-severe symptoms/late complications"<br>$CI_u < 0.80$<br>added benefit, extent: "considerable" |
| Constipation | Median: NA vs. 4.4 months<br>HR: 0.50 [0.32; 0.79]; p = 0.003<br>probability: "hint" | Outcome category "non-serious/non-severe symptoms/late complications"<br>$CI_u < 0.80$<br>added benefit, extent: "considerable" |

(continued)

Table 14: Extent of added benefit at outcome level: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation) (continued)

| **Outcome category**<br>**Outcome** | **Pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy[a]**<br>**Median time to event or proportion of events**<br>**Effect estimate [95% CI]; p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| EORTC QLQ-LC13 (symptom scales) – time to deterioration[d] | | |
| Dyspnoea | Median: 9.7 vs. 4.0 months<br>HR: 0.83 [0.55; 1.26]; p = 0.381 | Lesser benefit/added benefit not proven |
| Pain (chest) | Median: NA vs. NA months<br>HR: 0.60 [0.33; 1.07]; p = 0.084 | Lesser benefit/added benefit not proven |
| Pain (arm/shoulder) | Median: 11.8 vs. 8.3 months<br>HR: 0.82 [0.48; 1.39]; p = 0.459 | Lesser benefit/added benefit not proven |
| Pain (other) | Median: 7.6 vs. 6.1 months<br>HR: 0.72 [0.47; 1.10]; p = 0.126 | Lesser benefit/added benefit not proven |
| Cough | Median: NA vs. 8.2 months<br>HR: 0.64 [0.38; 1.06]; p = 0.085 | Lesser benefit/added benefit not proven |
| Haemoptysis | Median: NA vs. NA months<br>HR: 0.38 [0.15; 0.97]; p = 0.042 | Outcome category "non-serious/non-severe symptoms/late complications"<br>$0.90 \leq CI_u < 1.00$<br>Lesser benefit/added benefit not proven[e] |
| Alopecia | Median: NA vs. 3.4 months<br>HR: 0.09 [0.04; 0.19]; p < 0.001<br>probability: "hint" | Outcome category "non-serious/non-severe symptoms/late complications"<br>$CI_u < 0.80$<br>added benefit, extent: "considerable" |
| Dysphagia | Median: NA vs. 12.2 months<br>HR: 0.42 [0.23; 0.76]; p = 0.004<br>probability: "hint" | Outcome category "non-serious/non-severe symptoms/late complications"<br>$CI_u < 0.80$<br>added benefit, extent: "considerable" |
| Sore mouth | Median: NA vs. 7.2 months<br>HR: 0.31 [0.17; 0.55]; p < 0.001<br>probability: "hint" | Outcome category "non-serious/non-severe symptoms/late complications"<br>$CI_u < 0.80$<br>added benefit, extent: "considerable" |
| Peripheral neuropathy | Median: 13.8 vs. 5.7 months<br>HR: 0.47 [0.29; 0.75]; p = 0.002<br>probability: "hint" | Outcome category "non-serious/non-severe symptoms/late complications"<br>$CI_u < 0.80$<br>added benefit, extent: "considerable" |
| Health status (EQ-5D VAS) – time to deterioration | | |
| Responder criterion<br>10 points | Median: 9.7 vs. 3.7 months<br>HR: 0.61 [0.40; 0.92]; p = 0.018 | Non-serious/non-severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>Lesser benefit/added benefit not proven[e] |
| Responder criterion<br>7 points | Median: 3.6 vs. 1.9 months<br>HR: 0.68 [0.46; 1.01]; p = 0.055 | Lesser benefit/added benefit not proven |

(continued)

Table 14: Extent of added benefit at outcome level: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation) (continued)

| **Outcome category**<br>**Outcome** | **Pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy[a]**<br>**Median time to event or proportion of events**<br>**Effect estimate [95% CI]; p-value**<br>**Probability[b]** | **Derivation of extent[c]** |
|---|---|---|
| **Health-related quality of life** | | |
| EORTC QLQ-C30 (functional scales) – time to deterioration[d] | | |
| Global health status | Median: 7.8 vs. 3.0 months<br>HR: 0.69 [0.46; 1.04]; p = 0.079 | Lesser benefit/added benefit not proven |
| Emotional functioning | Median: NA vs. 10.7 months<br>HR: 0.60 [0.36; 1.00]; p = 0.052 | Lesser benefit/added benefit not proven |
| Cognitive functioning | Median: 15.4 vs. 4.6 months<br>HR: 0.71 [0.47; 1.10]; p = 0.123 | Lesser benefit/added benefit not proven |
| Physical functioning | Median: 8.5 vs. 1.8 months<br>HR: 0.48 [0.32; 0.71]; p < 0.001<br>probability: "hint" | Outcome category: quality of life<br>$CI_u < 0.75$, risk ≥ 5%<br>added benefit, extent: "major" |
| Role functioning | Median: NA vs. 4.0 months<br>HR: 0.56 [0.37; 0.85]; p = 0.006<br>probability: "hint" | Outcome category: quality of life<br>$0.75 < CI_u < 0.90$<br>added benefit, extent "considerable" |
| Social functioning | Median: NA vs. 2.2 months<br>HR: 0.42 [0.27; 0.64]; p < 0.001<br>probability: "hint" | Outcome category: quality of life<br>$CI_u < 0.75$, risk ≥ 5%<br>added benefit, extent: "major" |
| **Side effects** | | |
| SAEs | Median: 12.4 months vs. NA<br>HR: 0.87 [0.58; 1.30]; p = 0.503 | Greater/lesser harm not proven |
| Severe AEs<br>(CTCAE grade ≥ 3) | Median: 7.6 vs. 1.4 months<br>HR: 0.49 [0.34; 0.70]; p < 0.001<br>probability: "hint" | Outcome category: serious/severe side effects<br>$CI_u < 0.75$, risk ≥ 5%<br>lesser harm, extent: "major" |
| Discontinuation due to AEs | Proportion of events: 11.0% vs. 17.9%<br>RR: 0.61 [0.31; 1.20]; p = 0.154 | Greater/lesser harm not proven |
| Specific AEs | | |
| Immune-related AEs | No data available for the relevant subpopulation | |
| Immune-related SAEs | No data available for the relevant subpopulation | |
| Immune-related severe AEs (CTCAE grade ≥ 3) | No data available for the relevant subpopulation | |
| Further specific AEs | No data available for the relevant subpopulation | |

(continued)

Table 14: Extent of added benefit at outcome level: pembrolizumab vs. cisplatin- or carboplatin-based chemotherapy (relevant subpopulation) (continued)

a: Before randomization, chemotherapy was chosen for the individual patient from the following combination chemotherapies: cisplatin + gemcitabine, cisplatin + pemetrexed, carboplatin + gemcitabine, carboplatin + pemetrexed, carboplatin + paclitaxel.
b: Probability provided if a statistically significant and relevant effect is present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the $CI_u$.
d: The time to deterioration by at least 10 points is provided.
e: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
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; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

### 2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of pembrolizumab in comparison with a cisplatin- or carboplatin-based chemotherapy (relevant subpopulation)

| **Positive effects** | **Negative effects** |
|---|---|
| Mortality<br>▫ overall survival: indication of an added benefit – extent: “considerable” | – |
| Non-serious/non-severe symptoms/late complications<br>▫ symptoms: hint of an added benefit – extent: “considerable” (including nausea and vomiting, constipation, alopecia, dysphagia, sore mouth, peripheral neuropathy)<br>▫ symptoms: hint of an added benefit – extent: “minor” (including dyspnoea, appetite loss) | – |
| Health-related quality of life<br>▫ hint of an added benefit – extent: “major” (including physical functioning, social functioning)<br>▫ hint of an added benefit – extent: “considerable” (role functioning) | – |
| Serious/severe side effects<br>▫ severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: “major” | – |
| No results for immune-related side effects and on further specific AEs available in the relevant subpopulation | |
| AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events | |

In the overall consideration, there are only positive effects; no complete analyses for side effects were available for the relevant subpopulation, however.

On the positive side, there is an indication of a considerable added benefit for the outcome "overall survival". Regarding symptoms, there is a hint of a considerable added benefit in 6 outcomes (e.g. nausea and vomiting, dysphagia) and a hint of a minor added benefit for 2 outcomes (dyspnoea, appetite loss). For the outcome "severe AEs" (CTCAE grade ≥ 3), there is a hint of lesser harm with the extent "major". Finally, there is a hint of an added benefit for 3 dimensions of health-related quality of life (extent "considerable" to "major").

The EORTC QLQ-LC13 questionnaire is used for recording specific symptoms in lung cancer patients. The symptom subscales "alopecia", "dysphagia", "sore mouth" and "peripheral neuropathy" record typical side effects of the cytotoxic chemotherapy used in lung cancer and are recorded as symptoms by the EORTC QLQ-LC13 questionnaire [13]. Typical side effects of new drugs, e.g. immune-related AEs in pembrolizumab, in contrast, are currently not recorded with the EORTC QLQ-LC13. The same problem occurs in the symptom subscale "nausea and vomiting" of the cancer-specific EORTC QLQ-C30 questionnaire. It therefore has to be considered in the assessment that the advantages over the ACT in the outcome category "symptoms" might be based largely on a reduction in side effects of the cytotoxic chemotherapy. A conclusive assessment of the data from the category "symptoms" is not possible for the relevant subpopulation in the present assessment because there was no information on common AEs and survival time analyses at System Organ Class level for the outcomes on side effects. This information is required to check whether effects recorded with the EORTC questionnaires also appear in side effects.

**Derivation of the added benefit – uncertainties due to missing information for the relevant subpopulation and overall consideration**

***Incomplete analyses on side effects***

No usable data for the relevant subpopulation were available for immune-related side effects and specific AEs. The results of the total population showed a disadvantage of pembrolizumab for immune-related side effects (see Appendix A, Table 23, of the full dossier assessment). Also regarding the specific AEs that were also only available for the total population (Table 23), further negative effects of pembrolizumab (skin and subcutaneous tissue disorders, respiratory, thoracic and mediastinal disorders [SAEs]) were shown besides further positive effects (gastrointestinal disorders, metabolism and nutrition disorders, nervous system disorders, blood and lymphatic system disorders [CTCAE grade ≥ 3]). The effects of immune-related side effects and specific AEs in the relevant subpopulation were unclear. It was not assumed, however, that these completely outweighed the positive effects of pembrolizumab in severe AEs (CTCAE grade ≥ 3). Overall, a hint of lesser harm was assumed for the category "side effects" for the relevant subpopulation.

***Missing subgroup analyses***

Since there were no subgroup analyses for the relevant subpopulation, there was an uncertainty whether effect modifications also existed in this population. For the total population, an indication of an effect modification for the characteristic "sex" was shown for overall survival and proof of an effect modification by the characteristic "sex" for 3 further outcomes (see Appendix B, Table 24, of the full dossier assessment). In the total population, this would lead to a separate derivation of the added benefit for men and women.

***Insufficient information on the TPC interviews***

Missing details on the retrospective TPC interviews, i.e. on the quality of the subgroup formation from which the results for the relevant subpopulation were taken, added to the uncertainty (see also Section 2.3.2 and Section 2.7.2.4.1 of the full dossier assessment). There was no concrete information on the conduct of the interviews and on the distribution of the answers in the treatment groups. The subgroup presented by the company was used as an approximation for the relevant subpopulation, but an uncertainty remains whether the ACT was implemented adequately for all patients in this population.

***Overall consideration***

Hence in the overall consideration, on the positive side, there is an indication of an added benefit with the extent "considerable" in the category "mortality". In addition, there were further hints of an added benefit in the categories "morbidity" and "health-related quality of life" and in the category "side effects" for the outcome "severe AEs" (CTCAE grade $\geq 3$). Regarding side effects, there was a hint of lesser harm in the overall consideration.

Since the role of the effect modification by the characteristic "sex" in the relevant subpopulation remained unclear and there were additional principal uncertainties regarding the choice of the relevant subpopulation, the certainty of conclusions on the basis of available data was limited.

In summary, there is a hint of a considerable added benefit of pembrolizumab in comparison with the ACT cisplatin- or carboplatin-based chemotherapy for patients with first-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS $\geq 50\%$) without activating EGFR or ALK mutations.

The result of the assessment of the added benefit of pembrolizumab in comparison with the ACT is summarized in Table 16.

Table 16: Pembrolizumab – extent and probability of added benefit

| Therapeutic indication | ACT[a] | Extent and probability of added benefit |
|---|---|---|
| First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) without activating EGFR or ALK mutations in adults[b] | Patients with ECOG Performance Status 0, 1 or 2:<br>▪ **cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) under consideration of the approval status<br>*or*<br>▪ **carboplatin in combination with a third-generation cytostatic agent** (only for patients with increased risk of cisplatin-induced side effects in the framework of a combination therapy; see Appendix VI to Section K of the Pharmaceutical Directive [3])<br>*or*<br>▪ carboplatin in combination with nab-paclitaxel<br><br>Patients with ECOG Performance Status 2:<br>▪ as an alternative to the platinum-based combination therapy: monotherapy with gemcitabine or vinorelbine | Hint of considerable added benefit |

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: It is assumed for the present therapeutic indication that the NSCLC patients have stage IV disease (staging according to IASLC, UICC), without indication for curative resection, radiotherapy or radiochemotherapy.
ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; IASLC: International Association for the Study of Lung Cancer; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TPS: Tumour Proportion Score; UICC: Union for International Cancer Control

This deviates from the approach of the company, which, based on the total population of the KEYNOTE 024 study, derived an indication of a major added benefit for the present research question.

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

## 2.6 List of included studies

MSD 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 MK-3475; clinical study report [unpublished]. 2016.

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: 02.03.2017]. 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): full text view [online]. In: ClinicalTrials.gov. 15.11.2016 [Accessed: 02.03.2017]. URL: https://clinicaltrials.gov/show/NCT02142738.

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.

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

## References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22.04.2015 [Accessed: 01.06.2016]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.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]. 06.06.2016 [Accessed: 16.02.2017]. URL: https://www.g-ba.de/downloads/83-691-410/AM-RL-VI-Off-label-2016-06-08.pdf.

4. *MSD Sharp & Dohme. Fachinformation KEYTRUDA (Pembrolizumab) 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung; Stand: Februar 2017.

5. *Fresenius Kabi. Gemcitabin Kabi 38 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. 03.2015 [Accessed: 09.01.2017]. URL: http://www.fachinfo.de/.

6. *Medac. Cisplatin 0,5 mg/ml Lösung medac: Fachinformation [online]. 01.2014 [Accessed: 09.01.2017]. URL: http://www.fachinfo.de/.

7. *Accord Healthcare. Carboplatin Accord 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung: Wortlaut der für die Fachinformation vorgesehenen Angaben Fachinformation [online]. 04.2015 [Accessed: 09.01.2017]. URL: http://accord-healthcare.de/fileadmin/user_upload/Produkte/fachinformationen/FI_CarboplatinAccord_MR_13.4.2015.pdf.

8. Lilly. ALIMTA: Fachinformation [online]. 01.2017 [Accessed: 01.03.2017]. URL: https://www.fachinfo.de/.

9. *Hexal AG. Fachinformation Paclitaxel HEXAL (Paclitaxel) 6 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 01.2014 [Accessed: 09.01.2017]. URL: http://www.hexal.de/praeparate/otc/index_hxmod_id_353_ws_paclitaxel_med_paclitaxel-hexal.php?schnellinfos=true.

10. *Masters GA, Johnson DH, Temin S. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2016; 12: 90-93.

11. *Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27(Suppl 5): v1-v27.

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

13. *Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994; 30A(5): 635-642.

Citations marked with * are unedited citations provided by the company.

*The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-06-pembrolizumab-non-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.7830.html.*