Cemiplimab (NSCLC, combination with platinum-based chemotherapy)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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

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

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

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

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Jana Göbel
- Barbara Spix
- Benjamin Becker
- Claudia Kapp
- Maximilian Kind
- Prateek Mishra
- Katrin Nink
- Dominik Schierbaum
- Ulrike Seay

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Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of figures

Page

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
AM-RL	Arzneimittel-Richtlinie (Pharmaceutical Directive)
BSA	body surface area
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
nab	albumin-bound nanoparticles
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
ROS1	c-ros oncogene 1
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TPC	treatment of physician’s choice

I 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 cemiplimab (in combination with platinum-based chemotherapy). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 28 April 2023.

Research question

The aim of the present report is to assess the added benefit of cemiplimab in combination with platinum-based chemotherapy (hereinafter referred to as "cemiplimab + platinum-based chemotherapy") in comparison with the appropriate comparator therapy (ACT) for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing programmed cell death ligand 1 (PD-L1) in ≥ 1% of tumour cells, with no epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or c-ros oncogene 1 (ROS1) aberrations. Treatment is intended for:

- patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- patients with metastatic NSCLC.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of cemiplimab + platinum-based chemotherapy (multipage table)

Research question	**Therapeutic indication**	**ACT**[a]
1	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab as monotherapy**[c] or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC)

Table 2: Research questions of the benefit assessment of cemiplimab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[a]
2	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 1% and < 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy**[c] (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ **pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel**[c] (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0-1 and non-squamous NSCLC) or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive[d] (only for patients with ECOG PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients are not indicated for definitive chemoradiation or for definitive local therapy, and that no molecularly stratified therapy (against BRAF, KRAS G12C, METex14 or RET) is an option for the patients at the time of treatment with cemiplimab in combination with platinum-based chemotherapy.
c. In the present therapeutic indication, pembrolizumab is approved as monotherapy and in combination with platinum-containing chemotherapy only for patients with metastatic NSCLC.
d. Regarding carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive [1].

Table 2: Research questions of the benefit assessment of cemiplimab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[a]
ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; nab: albumin-bound nanoparticles; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1		

In this benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients with PD-L1 expression of tumour cells of ≥ 50%
- Research question 2: patients with PD-L1 expression of tumour cells from 1 to 49%

The company followed the G-BA's specification of the ACT and selected pembrolizumab as monotherapy for research question 1 (patients with PD-L1 expression of tumour cells of ≥ 50%). For research question 2 (patients with PD-L1 expression of tumour cells from 1 to 49%), the company initially named pembrolizumab in combination with platinum-based chemotherapy as ACT. It further specified this choice by naming pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy for patients with non-squamous NSCLC, and pembrolizumab in combination with carboplatin and either paclitaxel or albumin-bound nanoparticle (nab)-paclitaxel for patients with squamous NSCLC.

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

Research question 1: patients with PD-L1 expression of tumour cells of ≥ 50%

Study pool and study design

Concurring with the company's findings, the check of completeness of the study pool did not identify any study for a direct comparison of cemiplimab + platinum-based chemotherapy with the ACT.

Therefore, the company presented 2 adjusted indirect comparisons according to Bucher for the assessment of cemiplimab + platinum-based chemotherapy in comparison with pembrolizumab using platinum-based chemotherapy as common comparator. The choice of the common comparator is appropriate.

For the adjusted indirect comparisons, the company identified the EMPOWER-Lung 3 study on the intervention side, and the KEYNOTE 024 study as well as the KEYNOTE 042 study and its extension study KEYNOTE 042-China on the pembrolizumab side. Concurring with the company, the KEYNOTE 042-China study is not considered further because no patient characteristics of the relevant subpopulation (with PD-L1 expression of tumour cells of ≥ 50%) are available, so that the similarity with the other studies of the indirect comparison cannot be assessed.

Indirect comparisons presented by the company

The company divided the population of research question 1 (patients with PD-L1 expression of tumour cells of ≥ 50%) into 2 subpopulations based on NSCLC histology. The company justified this by stating that the results for the comparator side of the indirect comparison were only available separately according to histology. Irrespective of the question of whether these data are available, the company did not give any consideration to combining the results of the 2 indirect comparisons in accordance with the G-BA's research question.

For the adjusted indirect comparison of patients with non-squamous NSCLC, the company chose pemetrexed + carboplatin or cisplatin as common comparator and used a subpopulation of patients with PD-L1 expression of tumour cells of ≥ 50% and non-squamous NSCLC histology from the EMPOWER-Lung 3 study and the KEYNOTE 024 and KEYNOTE 042 studies. The company pooled the results of the KEYNOTE studies on the pembrolizumab side of the indirect comparison in a meta-analysis.

For the adjusted indirect comparison of patients with squamous NSCLC, the company chose paclitaxel + carboplatin as common comparator and used a subpopulation of patients with PD-L1 expression of tumour cells of ≥ 50% and squamous NSCLC histology from the EMPOWER-Lung 3 study and the KEYNOTE 042 study.

The indirect comparisons of the company cannot be used for the benefit assessment because the company only presented results for one outcome and because the subpopulations of the studies presented do not have the similarity required for an indirect comparison. This is explained below.

Study with cemiplimab + platinum-based chemotherapy: EMPOWER-Lung 3

The EMPOWER-Lung 3 study is an ongoing, double-blind RCT comparing cemiplimab + platinum-based chemotherapy with placebo + platinum-based chemotherapy. The study included adult patients with histologically or cytologically confirmed locally advanced NSCLC (stage IIIB and IIIC) or metastatic NSCLC (stage IV). Patients with stage IIIB and IIIC disease were not allowed to be candidates for definitive chemoradiation, patients with stage IV disease were not allowed to have received prior systemic treatment for the advanced or metastatic stage. Furthermore, molecular genetic testing had to prove that the patients did

not have EGFR mutations, ALK translocations or ROS1 fusions. Good general health status at study entry, corresponding to an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, was also required for enrolment.

The EMPOWER-Lung 3 study included a total of 466 patients, allocated in a 2:1 ratio either to treatment with cemiplimab + platinum-based chemotherapy (N = 312) or placebo + platinum-based chemotherapy (N = 154). The treatment options of platinum-based chemotherapy were pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin, or paclitaxel + carboplatin. Treatment with pemetrexed was only an option for patients with non-squamous histology.

The administration of cemiplimab and the platinum-based chemotherapy regimens largely corresponded to the specifications of the Summaries of Product Characteristics (SPCs).

Treatment was until disease progression, death, unacceptable toxicity, initiation of subsequent antineoplastic therapy or withdrawal of consent.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events (AEs).

The company presented results for 2 subpopulations. On the one hand, these were the results of patients with PD-L1 expression of tumour cells of ≥ 50% and non-squamous histology who were assigned to treatment with pemetrexed + carboplatin or cisplatin before randomization (48 in the intervention arm versus 21 in the comparator arm); on the other, the results of patients with PD-L1 expression of tumour cells of ≥ 50% and squamous histology who were assigned to treatment with paclitaxel + carboplatin before randomization (35 in the intervention arm versus 21 in the comparator arm). The company only presented results for the outcome of overall survival.

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

The KEYNOTE 024 study is a completed, open-label RCT comparing pembrolizumab with platinum-based chemotherapy. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation, whose tumours had PD-L1 expression ≥ 50%. The patients had to be in good general condition (according to an ECOG PS ≤ 1). Prior systemic antineoplastic treatment for the metastatic stage was not allowed.

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based chemotherapy (N = 151). The treatment options were as follows:

pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, or paclitaxel + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous histology.

The administration of pembrolizumab and the platinum-based chemotherapy regimens largely corresponded to the specifications of the SPCs.

Patients were treated until disease progression, unacceptable side effects, or study discontinuation upon the investigator's or patient's discretion.

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, outcomes on morbidity and health-related quality of life, and AEs.

The subpopulation presented by the company includes patients with non-squamous histology, PD-L1 expression in ≥ 50% of the tumour cells, and a chemotherapy regimen consisting of carboplatin + pemetrexed or cisplatin + pemetrexed. The company used analyses available from the benefit assessment procedure 2019-04-01-D-447 for this subpopulation. These analyses are limited to patients for whom, according to a retrospective investigator survey carried out by the company for the procedures of the time, carboplatin was a suitable treatment option in accordance with the specifications of the Pharmaceutical Directive (AM-RL) on off-label use (Appendix VI to Section K). The subpopulation is referred to as "treatment of physician's choice (TPC) population". This procedure means that 50 of 116 (43%) patients in the intervention and comparator arm who were assigned to therapy with carboplatin are not included in the analysis. In its dossier, the company only presented the results for the outcome of overall survival.

KEYNOTE 042

The KEYNOTE 042 study is a completed open-label RCT. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. The study included adults with histologically or cytologically confirmed diagnosis of NSCLC whose tumours expressed PD-L1 ≥ 1% and who were in the locally advanced or metastatic stage. Prior systemic treatment was not allowed in the study. For patients who had received adjuvant or neoadjuvant therapy, this treatment had to be completed 6 months prior to the development of metastases. Included patients had to have an ECOG PS of 0 or 1. The combination with pemetrexed was an option only for patients with non-squamous histology.

A total of 1274 patients were randomized in a 1:1 ratio either to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637). The administration of pembrolizumab and the platinum-based chemotherapy regimens largely corresponded to the specifications of the SPCs.

Patients were treated until disease progression, complete response, occurrence of unacceptable side effects or study discontinuation upon the investigator's or patient's discretion.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were AEs.

In its dossier, the company presented analyses for 2 subpopulations of the KEYNOTE 042 study. On the one hand, these were analyses for patients with non-squamous histology, PD-L1 expression in ≥ 50% of tumour cells, and a chemotherapy regimen consisting of carboplatin + pemetrexed; on the other, analyses for patients with squamous histology, PD-L1 expression in ≥ 50% of tumour cells, and a chemotherapy regimen consisting of carboplatin + paclitaxel. These analyses from the benefit assessment procedures 2019-04-01-D-447 + 2019-04-01-D-448 are available, but are limited to those patients for whom, according to a retrospective investigator survey carried out by the company for the procedures of the time, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K). The subpopulations are referred to as "TPC populations". This procedure means that 123 of 299 (41%) patients in the intervention and comparator arm with non-squamous NSCLC histology who were assigned to therapy with carboplatin are not included in the analysis. In the case of squamous histology, this limitation affects 61 out of 181 (34%) patients. The company used the TPC populations for the benefit assessment. In its dossier, the company only presented the results for the outcome of overall survival.

Similarity of the studies for the indirect comparison

Similarity of the study populations

In principle, the 3 studies EMPOWER-Lung 3, KEYNOTE 024 and KEYNOTE 042 have a similar study design. For the present indirect comparisons, the company chose platinum-based chemotherapy as common comparator. Different chemotherapy regimens were possible in the 3 included studies EMPOWER-Lung 3, KEYNOTE 024 and KEYNOTE 042. To enable an indirect comparison, the company therefore limited these regimens to individual treatment options. For patients with non-squamous NSCLC histology, the company used those subpopulations from the EMPOWER-Lung 3, KEYNOTE-024 and KEYNOTE 042 studies whose platinum-based chemotherapy consisted of pemetrexed + carboplatin or pemetrexed + cisplatin. For patients with squamous NSCLC histology, the company restricted the subpopulations of the EMPOWER-Lung 3 and KEYNOTE 042 studies based on the carboplatin + paclitaxel chemotherapy regimen specified by the company. To form the corresponding subpopulations from both KEYNOTE studies, the company additionally only used the results of those patients for whom, according to a retrospective survey, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K). The previously described post-hoc limitations based on the

chemotherapy regimen and retrospective survey on carboplatin result in relevant proportions of the study populations of the KEYNOTE studies not being included in the analyses. In the EMPOWER-Lung 3 study, the company did not make such a post-hoc restriction of the populations based on the use of carboplatin in accordance with the AM-RL on off-label use (Appendix VI to Section K). Thus, it can be assumed that the presented subpopulations of the KEYNOTE 024 and KEYNOTE 042 studies differ to a relevant extent from the subpopulation of the EMPOWER-Lung 3 study.

Usability of the indirect comparisons presented by the company

There is a relevant difference between the subpopulations of the KEYNOTE 024 and KEYNOTE 042 studies and the subpopulation of the EMPOWER-Lung 3 study due to the post-hoc restriction to those patients for whom, according to a retrospective survey, carboplatin was a suitable treatment option in accordance with the AM-RL on off-label use (Appendix VI to Section K). Thus, the similarity of the subpopulations for the indirect comparison is not given.

Furthermore, the company presented results for the indirect comparisons only for the outcome of overall survival. For this reason alone, no sufficient data is available for balancing benefit and harm. The analyses presented by the company cannot be used for the benefit assessment.

Research question 2: patients with PD-L1 expression of tumour cells from 1 to 49%

Study design and study pool

Concurring with the company's findings, the check of completeness of the study pool did not identify any study for a direct comparison of cemiplimab with the ACT.

The company therefore presented 2 adjusted indirect comparisons according to Bucher for the assessment of cemiplimab + platinum-based chemotherapy compared with pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1 and non-squamous histology), or pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG PS 0–1 and squamous histology) using platinum-based chemotherapy as common comparator. The choice of the common comparator is appropriate. In the following, the 2 ACTs selected by the company are referred to with the simplified term "pembrolizumab + platinum-based chemotherapy".

For the adjusted indirect comparisons, the company identified the EMPOWER-Lung 3 study on the intervention side, and the RCTs KEYNOTE 189, KEYNOTE 189-Japan, KEYNOTE 021G, KEYNOTE 407 and KEYNOTE 407-China for pembrolizumab + platinum-based chemotherapy. Concurring with the company, the studies KEYNOTE 189-Japan, KEYNOTE 021G and

KEYNOTE 407-China are not considered further because no data are available for the relevant subpopulation (PD-L1 expression of tumour cells from 1 to 49%), so that the similarity with the other studies of the indirect comparison cannot be assessed.

Indirect comparisons presented by the company

Since the KEYNOTE 189 study only included patients with non-squamous NSCLC and the KEYNOTE 407 study only included patients with squamous NSCLC, the company subdivided the population of research question 2 (patients with PD-L1 expression of the tumour cells from 1 to 49%) into 2 subpopulations based on NSCLC histology. However, the company did not give any consideration to combining the results of the 2 indirect comparisons in accordance with the G-BA's research question.

For the adjusted indirect comparison of patients with non-squamous NSCLC, the company chose pemetrexed + carboplatin or cisplatin as common comparator and used a subpopulation of the EMPOWER-Lung 3 study and the KEYNOTE 189 study.

For the adjusted indirect comparison of patients with squamous NSCLC, the company chose paclitaxel + carboplatin as common comparator and used a subpopulation of the EMPOWER-Lung 3 study and the KEYNOTE 407 study.

The indirect comparisons of the company cannot be used for the benefit assessment because the company only presented results for one outcome and because the subpopulations of the studies presented do not have the similarity required for an indirect comparison. This is explained below.

Study with cemiplimab + platinum-based chemotherapy: EMPOWER-Lung 3

The study description of the EMPOWER-Lung 3 study can be found in research question 1.

According to the approval of cemiplimab + platinum-based chemotherapy, first-line treatment is limited to adult patients with NSCLC expressing PD-L1 in ≥ 1% of tumour cells. For the EMPOWER-Lung 3 study, the company therefore presented data of the subpopulation of patients with PD-L1 expression of the tumour cells from 1 to 49%. To ensure better comparability, the company additionally restricted the patient population for the adjusted indirect comparison with regard to the chemotherapy regimen administered. For this purpose, in the case of non-squamous histology, it only considered patients who had been assigned to a chemotherapy combination of pemetrexed and carboplatin or cisplatin before randomization, and in the case of squamous histology, it only considered patients who had been assigned to a chemotherapy combination of paclitaxel and carboplatin before randomization.

The subpopulation with non-squamous NSCLC histology thus comprises 53 patients in the intervention arm versus 22 in the comparator arm; and the subpopulation with squamous NSCLC histology comprises 49 patients in the intervention arm versus 23 in the comparator arm.

Overall, in addition to the patient characteristics, the company only presented the result of the primary outcome of overall survival for the subpopulations, however. Results for the outcome categories of morbidity, health-related quality of life and side effects are not available in Module 4 E.

Studies with the ACT: KEYNOTE 189 and KEYNOTE 407

Study KEYNOTE 189

The KEYNOTE 189 study is an ongoing, RCT comparing pembrolizumab + platinum-based chemotherapy with platinum-based chemotherapy. The study included adults with histologically or cytologically confirmed stage IV non-squamous NSCLC without EGFR mutation or ALK translocation and ECOG PS ≤ 1 irrespective of the PD-L1 expression. Prior systemic treatment against stage IV NSCLC was not allowed.

The KEYNOTE 189 study included a total of 616 patients, randomized in a 2:1 ratio either to treatment with pembrolizumab in combination with carboplatin or cisplatin, and in each case pemetrexed (N = 410), or to treatment with only carboplatin or cisplatin, and in each case pemetrexed (N = 206).

The administration of pembrolizumab and the platinum-based chemotherapy regimens corresponded to the specifications of the SPCs.

Patients were treated until disease progression, unacceptable side effects, or treatment discontinuation upon the investigator's or patient's discretion.

The primary outcomes of the KEYNOTE 189 study are PFS and overall survival. Further patient-relevant outcomes are outcomes on morbidity, health-related quality of life and AEs.

Study KEYNOTE 407

The KEYNOTE 407 study is an ongoing, RCT comparing pembrolizumab + carboplatin-based chemotherapy with carboplatin-based chemotherapy. The study included adults with histologically or cytologically confirmed diagnosis of squamous NSCLC in the metastatic stage (stage IV). Patients had to have received no prior systemic treatment for this stage. For patients who had received adjuvant or neoadjuvant therapy, this treatment had to be completed at least 12 months prior to the development of metastases. Included patients had to have an ECOG PS of 0 or 1.

The study included a total of 559 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab + carboplatin-based chemotherapy (N = 278) or carboplatin-based chemotherapy (N = 281).

The administration of pembrolizumab and the platinum-based chemotherapy regimens largely correspond to the specifications of the SPCs.

Patients are treated until disease progression, complete response, unacceptable side effects, or study discontinuation upon the physician's or patient's discretion.

The primary outcomes of the study are PFS and overall survival. Patient-relevant secondary outcomes are morbidity, health-related quality of life, and AEs.

Subpopulations of the studies KEYNOTE 189 and KEYNOTE 407 presented by the company

From the studies on the comparator side of the indirect comparison, there is also only a subpopulation relevant in each case. In contrast to cemiplimab + platinum-based chemotherapy, the administration of pembrolizumab + platinum-based chemotherapy is approved in NSCLC regardless of PD-L1 expression. The KEYNOTE 189 study included patients with a PD-L1 expression of the tumour cells of < 50%, whereas the KEYNOTE 407 study included patients irrespective of the PD-L1 expression of the tumour cells. Patients with PD-L1 expression of tumour cells from 1 to 49% are relevant for the benefit assessment.

However, the company used the subpopulations of both KEYNOTE studies, which had already been used in the previous benefit assessment procedures 2019-04-01-D-447 + 2019-04-01-D-448. Both subpopulations were limited to patients with PD-L1 expression of tumour cells of < 50% for whom, according to a retrospective investigator survey carried out by the company for the procedures of the time, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K). These subpopulations were referred to as "TPC populations". This procedure means that 126 of 260 (48%) patients in the intervention and comparator arm with non-squamous NSCLC histology (KEYNOTE 189) who were assigned to therapy with carboplatin are not included in the analysis. In the case of squamous histology (KEYNOTE 407), this limitation affects 91 out of 401 (23%) patients. For the benefit assessment, the company used the TPC populations, which also include patients with a PD-L1 expression of the tumour cells of < 1%, however. This approach is not appropriate and is explained below.

Similarity of the studies for the indirect comparison

Similarity of the study populations

In principle, the 3 studies EMPOWER-Lung 3, KEYNOTE 189 and KEYNOTE 407 have a similar study design. However, it can be assumed that the study populations are not similar enough for an indirect comparison. This is due to the fact that the study populations of the KEYNOTE

studies include a relevant number of patients who are not included in the research question. Based on the approval of cemiplimab + platinum-based chemotherapy, patients with a PD-L1 expression of the tumour cells of 1 to 49% are relevant for the present research question. However, the proportion of patients with a PD-L1 expression of the tumour cells of < 1%, who are therefore not part of the research question, is 49% in the intervention versus 52% in the comparator arm in the KEYNOTE 189 study, and 45% versus 50% in the KEYNOTE 407 study. The approach of the company to include patients with a PD-L1 expression of tumour cells of < 1% in the similarity test is not appropriate.

Moreover, analogous to research question 1, it must be assumed that there is a relevant difference in the study populations between the KEYNOTE 189 and KEYNOTE 407 studies and the EMPOWER-Lung 3 study due to the post-hoc restriction of the subpopulation to those patients for whom, according to a retrospective survey, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K).

Usability of the indirect comparisons presented by the company

In summary, in particular the post-hoc restriction of the subpopulation described above and the high proportion of patients on the comparator side of the indirect comparison, which is not covered by research question 2, mean that the subpopulations presented are not similar enough for an indirect comparison, and therefore the 2 indirect comparisons of cemiplimab + platinum-based chemotherapy in comparison with the ACT presented by the company are not usable.

Besides, the company presented results for the indirect comparisons only for the outcome of overall survival. For this reason alone, no sufficient data is available for balancing benefit and harm. The analyses presented by the company cannot be used for the benefit assessment.

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

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

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

Research question 1: patients with PD-L1 expression of tumour cells of ≥ 50%

The data presented by the company for the assessment of the added benefit of cemiplimab + platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or with metastatic NSCLC expressing PD-L1 in ≥ 50% of tumour cells, with no EGFR, ALK or ROS1 aberrations, are not suitable for deriving an added benefit of cemiplimab + platinum-based chemotherapy compared with the ACT. An added benefit of cemiplimab + platinum-based chemotherapy for these patients is therefore not proven.

Research question 2: patients with PD-L1 expression of tumour cells from 1 to 49%

The data presented by the company for the assessment of the added benefit of cemiplimab + platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or with metastatic NSCLC expressing PD-L1 in 1 to ≥ 49% of tumour cells, with no EGFR, ALK or ROS1 aberrations, are not suitable for deriving an added benefit of cemiplimab + platinum-based chemotherapy compared with the ACT. An added benefit for these patients is therefore not proven.

Table 3 shows a summary of the probability and extent of added benefit of cemiplimab + platinum-based chemotherapy.

Table 3: Cemiplimab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**
1	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab as monotherapy**[c] or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC)	Added benefit not proven[d]

Table 3: Cemiplimab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 1% and < 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy**[c] (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ **pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel**[c] (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive[e] (only for patients with ECOG PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)	Added benefit not proven[d]

Table 3: Cemiplimab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients are not indicated for definitive chemoradiation or for definitive local therapy, and that no molecularly stratified therapy (against BRAF, KRAS G12C, METex14 or RET) is an option for the patients at the time of treatment with cemiplimab in combination with platinum-based chemotherapy.
c. In the present therapeutic indication, pembrolizumab is approved as monotherapy and in combination with platinum-containing chemotherapy only for patients with metastatic NSCLC.
d. Only patients with an ECOG PS of 0 or 1 were included in the studies for the indirect comparison.
e. Regarding carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive [1].

ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; nab: albumin-bound nanoparticles; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of cemiplimab in combination with platinum-based chemotherapy (hereinafter referred to as "cemiplimab + platinum-based chemotherapy") in comparison with the ACT for the first-line treatment of adult patients with NSCLC expressing PD-L1 in ≥ 1% of tumour cells, with no EGFR, ALK or ROS1 aberrations. Treatment is intended for:

- patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- patients with metastatic NSCLC.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of cemiplimab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[a]
1	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab as monotherapy**[c] or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC)

Table 4: Research questions of the benefit assessment of cemiplimab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[a]
2	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 1% and < 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy**[c] (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ **pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel**[c] (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive[d] (only for patients with ECOG PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients are not indicated for definitive chemoradiation or for definitive local therapy, and that no molecularly stratified therapy (against BRAF, KRAS G12C, METex14 or RET) is an option for the patients at the time of treatment with cemiplimab in combination with platinum-based chemotherapy.
c. In the present therapeutic indication, pembrolizumab is approved as monotherapy and in combination with platinum-containing chemotherapy only for patients with metastatic NSCLC.
d. Regarding carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive [1].

Table 4: Research questions of the benefit assessment of cemiplimab + platinum-based chemotherapy (multipage table)

Research question	Therapeutic indication	ACT[a]
ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; nab: albumin-bound nanoparticles; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1		

In this benefit assessment, the following terms are used for the patient populations of the 2 research questions:

- Research question 1: patients with PD-L1 expression of tumour cells of ≥ 50%
- Research question 2: patients with PD-L1 expression of tumour cells from 1 to 49%

The company largely followed the G-BA's specification of the ACT and selected pembrolizumab as monotherapy for research question 1 (patients with PD-L1 expression of tumour cells of ≥ 50%). For research question 2 (patients with PD-L1 expression of tumour cells from 1 to 49%), the company initially named pembrolizumab in combination with platinum-based chemotherapy as ACT. It further specified this choice by naming pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy for patients with non-squamous NSCLC, and pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for patients with squamous NSCLC.

The company deviated from the ACT for research questions 1 and 2 in individual aspects. However, these deviations of the company remain without consequence for the benefit assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 3 Research question 1: patients with PD-L1 expression of tumour cells of ≥ 50%

I 3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on cemiplimab (status: 15 February 2023)
- bibliographical literature search on cemiplimab (last search on 15 February 2023)
- search in trial registries/trial results databases for studies on cemiplimab (last search on 15 February 2023)
- search on the G-BA website for cemiplimab (last search on 15 February 2023)
- bibliographical literature search on the ACT (last search on 15 February 2023)
- search in trial registries/trial results databases for studies on the ACT (last search on 15 February 2023)
- search on the G-BA website for the ACT (last search on 15 February 2023)

To check the completeness of the study pool:

- search in trial registries for studies on cemiplimab (last search on 3 May 2023); for search strategies, see I Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 4 May 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company's findings, the check of completeness of the study pool did not identify any study for a direct comparison of cemiplimab with the ACT.

Therefore, the company presented 2 adjusted indirect comparisons according to Bucher [4] for the assessment of cemiplimab + platinum-based chemotherapy in comparison with pembrolizumab as monotherapy using platinum-based chemotherapy as common comparator. The company justified the choice of the common comparator by stating that the identified EMPOWER-Lung 3 study with the drug to be assessed (cemiplimab + platinum-based chemotherapy versus platinum-based chemotherapy) was the only RCT in the relevant therapeutic indication, and that therefore a comparison with the ACT specified by the G-BA (pembrolizumab) was only possible with a platinum-based chemotherapy as common comparator. The choice of the common comparator is appropriate.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparisons presented by the company.

I 3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Cemiplimab + platinum-based chemotherapy vs. platinum-based chemotherapy						
EMPOWER-Lung 3[d] (R2810-ONC-16113)	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8-11]
Pembrolizumab vs. platinum-based chemotherapy						
KEYNOTE 024	No	No	Yes	No	Yes [12,13]	Yes [14-28]
KEYNOTE 042	No	No	Yes	No	Yes [29,30]	Yes [22-28,31-35]
KEYNOTE 042-China	No	No	Yes	No	Yes [36]	Yes [37]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this designation.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool concurs with that of the company.

The company's study pool comprised the approval study EMPOWER-Lung 3 for cemiplimab + platinum-based chemotherapy, and the RCTs KEYNOTE 024 and KEYNOTE 042, as well as KEYNOTE 042-China for pembrolizumab as monotherapy.

The EMPOWER-Lung 3 study is a 2-part RCT. Both parts are independent of each other. Part 1 is an open-label, 3-arm study comparing cemiplimab + platinum-based chemotherapy + ipilimumab or cemiplimab + platinum-based chemotherapy with placebo + platinum-based chemotherapy in patients with PD-L1 expression in < 50% of tumour cells. The company excluded part 1 of the EMPOWER-Lung 3 study and only used part 2 for the benefit assessment. It justified this with the fact that part 1 of the study had not yet been completed and thus no results were available. This approach is appropriate. In the following, only part 2 of the EMPOWER-Lung 3 study is considered for the benefit assessment.

The extension study KEYNOTE 042-China was conducted in accordance with the same study protocol as the KEYNOTE 042 study. As no information on the patient characteristics of the relevant subpopulation (with PD-L1 expression of tumour cells of ≥ 50%) was available for the KEYNOTE 042-China study, the company did not consider this study in the indirect comparison. This approach is comprehensible, because a sufficient similarity of the patient populations in the studies in the indirect comparison is one of the prerequisites for a consideration of KEYNOTE 042-China in the indirect comparison. The similarity cannot be tested without the information on the relevant subpopulation. The KEYNOTE 042-China study is not considered below.

Figure 1 shows a schematic representation of the adjusted indirect comparison.

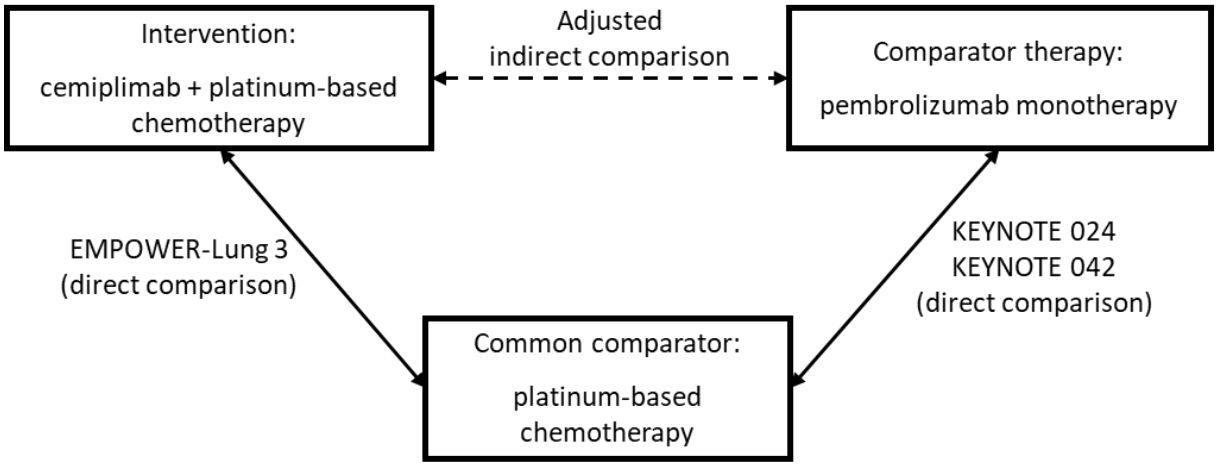

Figure 1: Study pool for the adjusted indirect comparison between cemiplimab + platinum-based chemotherapy and pembrolizumab monotherapy using platinum-based chemotherapy as the common comparator (patients with a PD L1 expression of tumour cells of ≥ 50%)

Indirect comparisons presented by the company

The company divided the population of research question 1 (patients with PD-L1 expression of tumour cells of ≥ 50%) into 2 subpopulations based on NSCLC histology. The company justified this by stating that the results for the comparator side of the indirect comparison were only available separately according to histology. Irrespective of the question of whether these data are available, the company did not give any consideration to combining the results of the 2 indirect comparisons in accordance with the G-BA's research question. The adjusted indirect comparisons submitted by the company are presented below:

- For patients with a PD-L1 expression of the tumour cells of ≥ 50% and non-squamous NSCLC, the company presented an indirect comparison using pemetrexed in combination with carboplatin or cisplatin as common comparator.

- For patients with a PD-L1 expression of the tumour cells of ≥ 50% and squamous NSCLC, the company presented an indirect comparison using paclitaxel in combination with carboplatin as common comparator.

For the adjusted indirect comparison of patients with non-squamous NSCLC, the company used a subpopulation of patients with PD-L1 expression of tumour cells of ≥ 50% and non-squamous NSCLC histology from the EMPOWER-Lung 3 study and the KEYNOTE 024 and KEYNOTE 042 studies. The company pooled the results of the KEYNOTE studies on the pembrolizumab side of the indirect comparison in a meta-analysis. Figure 2 shows a schematic representation of the adjusted indirect comparison.

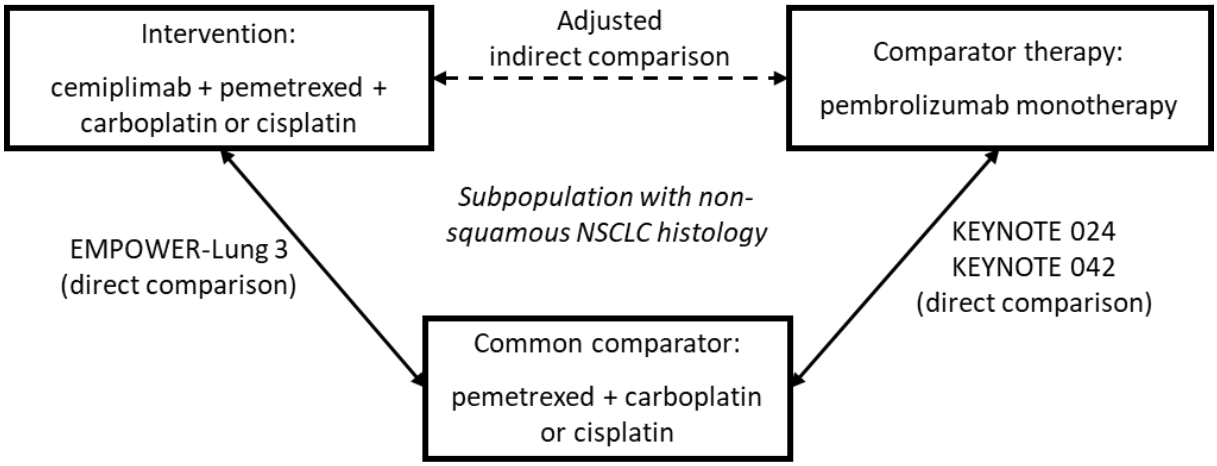

Figure 2: Study pool for the indirect comparison between cemiplimab + platinum-based chemotherapy and pembrolizumab monotherapy using platinum-based chemotherapy as the common comparator (patients with non-squamous NSCLC histology)

For the adjusted indirect comparison of patients with squamous NSCLC, the company used a subpopulation of patients with PD-L1 expression of tumour cells of ≥ 50% and squamous NSCLC histology from the EMPOWER-Lung 3 study and the KEYNOTE 042 study. Figure 3 shows a schematic representation of the adjusted indirect comparison.

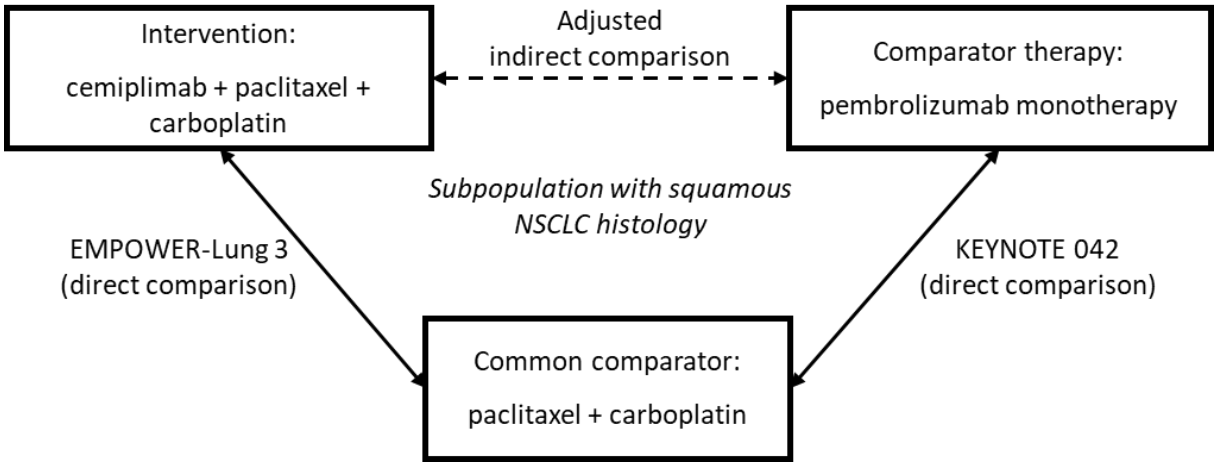

Figure 3: Study pool for the indirect comparison between cemiplimab + platinum-based chemotherapy and pembrolizumab monotherapy using platinum-based chemotherapy as the common comparator (patients with squamous NSCLC histology)

The company presented results of the indirect comparisons only for the outcome of overall survival

The company only presented results for the outcome of overall survival for both indirect comparisons. Results for the outcome categories of morbidity, health-related quality of life and side effects are not available in Module 4 E. The company justified its approach by stating that the results of the studies KEYNOTE 024 and KEYNOTE 042 had a high risk of bias due to the open-label study design and therefore could not be used for an indirect comparison. The approach of the company is not appropriate. The results of the patient-relevant outcomes in the indirect comparison are required to be able to make an appropriate balancing of benefit and harm. The risk of bias and the associated interpretability of the results are assessed for each outcome. For this reason alone, no sufficient data is available for balancing benefit and harm.

Similarity of the study population is not given, and analyses presented by the company are not usable for the indirect comparison

The similarity of the study populations is not given. The main reason for this is that the company used a retrospectively restricted subpopulation of the KEYNOTE 024 and KEYNOTE 042 studies from previous benefit assessment procedures. Due to this restriction, only those patients were considered for whom carboplatin was a suitable treatment option in accordance with the AM-RL on off-label use (Appendix VI to Section K [1]). It can be assumed that there is a relevant difference between the relevant subpopulation of the EMPOWER-Lung 3 study and the presented subpopulations of the KEYNOTE 024 and KEYNOTE 042 studies. In addition, further aspects cannot be assessed with sufficient certainty for the

evaluation of the similarity of the studies due to missing data (treatment duration and observation period as well as subsequent therapies) (see Section I 3.1.2).

The analyses presented by the company cannot be used for the benefit assessment. This is explained below.

I 3.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Cemiplimab + platinum-based chemotherapy vs. platinum-based chemotherapy						
EMPOWER-Lung 3	RCT, double-blind, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed NSCLC, squamous or non-squamous, without EGFR mutation, ALK or ROS1 translocation, ECOG PS ≤ 1 ▪ stage IIIB or IIIC and not candidates for definitive chemoradiation, or ▪ stage IV, without previous systemic therapy[b, c]	Cemiplimab + platinum-based chemotherapy[d] (N = 312) Placebo + platinum-based chemotherapy[d] (N = 154) <u>Subpopulation thereof analysed by the company[e]:</u> ▪ PD-L1 expression ≥ 50%, non-squamous ▫ Cemiplimab + pemetrexed + carboplatin or cisplatin (n = 48) ▫ Placebo + pemetrexed + carboplatin or cisplatin (n = 21) ▪ PD-L1 expression ≥ 50%, squamous ▫ Cemiplimab + paclitaxel + carboplatin (n = 35) ▫ Placebo + paclitaxel + carboplatin (n = 21)	Screening: 28 days before randomization Treatment: until progression, death, withdrawal of consent, unacceptable toxicity, initiation of other subsequent antineoplastic therapy, or after a maximum of 108 weeks of cemiplimab Observation: outcome-specific, at most until death (for the outcome of overall survival)	74 centres in: China, Georgia, Greece, Malaysia, Poland, Romania, Russia, Thailand, Turkey, Ukraine 31 May 2019–ongoing Data cut-offs: 3 January 2021[f] 14 June 2021[g] 14 June 2022[h]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Pembrolizumab vs. platinum-based chemotherapy						
KEYNOTE 024	RCT, open-label, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed stage IV NSCLC, PD-L1 expressing tumours (TPS ≥ 50%) without EGFR mutation, without ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[b, c]	Pembrolizumab (N = 154) platinum-based chemotherapy (N = 151) Subpopulation thereof presented by the company (TPC survey population)[e, i]: ▪ non-squamous ▫ pembrolizumab (n = 75) ▫ pemetrexed + carboplatin or cisplatin (n = 74)	Screening: 30 days prior to the start of treatment Treatment: until progression, unacceptable side effects, study discontinuation upon the investigator's or patient's discretion, complete response, or a maximum of 35 cycles of pembrolizumab[j] Observation: outcome-specific, at most until death (for the outcome of overall survival)	142 centres in: Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, United Kingdom, USA 9/2014–5/2016[k] Data cut-offs: 9 May 2016[k] 10 July 2017 (final analysis on overall survival) 1 June 2020 (analysis on 5-year overall survival)	Primary: PFS Secondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 042	RCT, open-label, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed, locally advanced or metastatic NSCLC, PD-L1 expressing tumours (TPS ≥ 1%) without EGFR mutation, without ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[b, c]	Pembrolizumab (N = 637) platinum-based chemotherapy (N = 637) Subpopulation thereof presented by the company (TPC survey population)[e, i]: ▪ PD-L1 expression ≥ 50%, non-squamous ▫ pembrolizumab (n = 90) ▫ pemetrexed + carboplatin or cisplatin (n = 86) ▪ PD-L1 expression ≥ 50%, squamous ▫ pembrolizumab (n = 57) ▫ paclitaxel + carboplatin (n = 63)	Screening: 30 days prior to the start of treatment Treatment: until progression, unacceptable side effects, study discontinuation upon the investigator's or patient's discretion, complete response, or a maximum of 35 cycles of pembrolizumab[j] Follow-up: outcome-specific, at most until death (for the outcome of overall survival)	196 centres in: Argentina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Czech Republic, Estonia, Guatemala, Hong Kong, Hungary, Japan, Latvia, Lithuania, Malaysia, Mexico, Peru, Philippines, Poland, Portugal, Romania, Russia, South Africa, South Korea, Sweden, Switzerland, Taiwan, Thailand, Turkey, Ukraine, Vietnam 11/2014–9/2022 Data cut-offs: 26 February 2018 4 September 2018 (final PFS analysis)	Primary: overall survival Secondary: AEs

Table 6: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on outcomes relevant for this benefit assessment. b. For patients who had received neoadjuvant or adjuvant treatment, the last treatment had to be completed at least 6 months prior to the diagnosis of the metastatic disease. c. Without prior systemic therapy for the metastatic NSCLC stage (KEYNOTE 024) or the advanced or metastatic NSCLC stage (KEYNOTE 042, EMPOWER-Lung 3). d. Prior to randomization, a choice for the individual patient was made at the investigator's discretion, according to the local standard of care, between the following platinum-based chemotherapies: pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin, paclitaxel + carboplatin. Combinations with pemetrexed were only allowed for patients with non-squamous histology. e. For the adjusted indirect comparison in non-squamous histology, only patients were considered who had been assigned to platinum-based chemotherapy consisting of carboplatin + pemetrexed or cisplatin + pemetrexed (KEYNOTE 024, EMPOWER-Lung 3) or carboplatin + pemetrexed (KEYNOTE 042) prior to randomization. For the adjusted indirect comparison in squamous histology, only patients were considered who had been assigned to platinum-based chemotherapy consisting of carboplatin + paclitaxel (KEYNOTE 042, EMPOWER-Lung 3) prior to randomization. f. First planned interim analysis after about 146 deaths (50%). g. Second planned interim analysis after about 204 deaths (70%), primary analysis. h. 2 post-hoc analyses were conducted on this data cut-off. With the second post-hoc analysis, the primary analysis was updated to the therapeutic indication approved by the EMA and thus restricted to patients with a PD-L1 expression of the tumour cells of ≥ 1%. i. The subpopulation comprises patients who, according to the results of the TPC survey by the company, were treated in accordance with the criteria of the AM-RL for the off-label use (Appendix VI to Section K [1]) of carboplatin and have a PD-L1 expression in ≥ 50% of tumour cells. j. Patients in the pembrolizumab arm (KEYNOTE 024 and KEYNOTE 042) could temporarily discontinue treatment after confirmed complete response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab at the investigator's discretion after subsequent confirmed progression (if certain conditions regarding previous treatment duration and disease status were met) ("second course phase"). Based on the study documents, it can be assumed that only < 5% of the patients in the total study population (KEYNOTE 024 and KEYNOTE 042) reached the "second course phase". k. Since pembrolizumab was superior to platinum-based chemotherapy with respect to overall survival, the study was stopped at the time point of the data cut-off of the second interim analysis (9 May 2016). This second data cut-off was prospectively planned to be performed after 175 events for the outcome of PFS had been reached. All patients in the treatment arm with solely platinum-based chemotherapy were offered to switch to the pembrolizumab arm.						

Table 6: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AE: adverse event; ALK: anaplastic lymphoma kinase; AM-RL: Pharmaceutical Directive; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; n: subpopulation analysed and presented by the company; 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; ROS1: c-ros oncogene 1; TPC: treatment of physician's choice						

Table 7: Characteristics of the intervention – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Intervention	Comparison
Cemiplimab + platinum-based chemotherapy vs. platinum-based chemotherapy		
EMPOWER-Lung 3	Cemiplimab 350 mg, IV (as 30-minute infusion), following platinum-based chemotherapy, IV, on day 1 of a 21-day cycle	Placebo as IV infusion, following platinum-based chemotherapy, IV, on day 1 of a 21-day cycle
	Therapy regimen – platinum-based chemotherapy[a] Induction therapy, 4 cycles Squamous and non-squamous ▫ paclitaxel 200 mg/m² BSA, IV + carboplatin AUC of 5 or 6 mg/mL/min, IV, on day 1 of each 21-day cycle *or* ▫ paclitaxel 200 mg/m² BSA, IV + cisplatin 75 mg/m² BSA, IV, on day 1 of each 21-day cycle *or* Only non-squamous: ▫ pemetrexed 500 mg/m² BSA, IV + carboplatin AUC of 5 or 6 mg/mL/min, IV, on day 1 of each 21-day cycle *or* ▫ pemetrexed 500 mg/m² BSA, IV + cisplatin 75 mg/m² BSA, IV, on day 1 of each 21-day cycle Maintenance phase Only non-squamous: ▫ After 4 cycles of pemetrexed + cisplatin or pemetrexed + carboplatin, further treatment with pemetrexed 500 mg/m² BSA, IV, on day 1 of a 21-day cycle was mandatory	
	Dose adjustments ▪ Cemiplimab: no dose adjustment allowed; treatment interruptions ≤ 84 days due to toxicity allowed[b] ▪ Platinum-based chemotherapy: dose adjustments allowed according to regional guidelines	
	Permitted pretreatment ▪ adjuvant or neoadjuvant platinum-based chemotherapy (following surgery and/or radiotherapy) ≥ 6 months before the development of recurrent or metastatic disease **Non-permitted pretreatment** ▪ systemic therapy for stage IV NSCLC ▪ other investigational products ≤ 30 days prior to study inclusion or ≤ 5 half-lives of the investigational product ▪ anti-PD-1 or anti-PD-L1 drugs ▪ other immunomodulators (e.g. antibodies against CTLA-4) ≤ 6 months prior to the first dose of study medication ▪ systemic corticosteroids (> 10 mg prednisone/day or equivalent)c ≤ 14 days prior to randomization ▪ live vaccines ≤ 30 days prior to the first dose of study medication	

Table 7: Characteristics of the intervention – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Intervention	Comparison
EMPOWER -Lung 3 (continued)	**Premedication** ▪ For cemiplimab: only for infusion-related reactions (from cycle 2) diphenhydramine or equivalent and/or paracetamol, corticosteroids if necessary ▪ For platinum-based chemotherapy with paclitaxel: corticosteroids, diphenhydramine + H2 receptor antagonists ▪ For platinum-based chemotherapy with pemetrexed: corticosteroids, folic acid and vitamin B12[d] ▪ For cisplatin-based chemotherapy: adequate hydration and highly effective anti-emetic combination therapy **Concomitant treatment** ▪ bisphosphonates, denosumab for the treatment of bone metastasis allowed ▪ short-term use of systemic corticosteroids allowed for prophylaxis or treatment of non-autoimmune diseases	
Pembrolizumab vs. platinum-based chemotherapy		
KEYNOTE 024	Pembrolizumab 200 mg IV (as 30-minute infusion) on day 1 of a 21-day cycle	Platinum-based chemotherapy[a] for 4 to 6 cycles: <u>Induction phase (4 to 6 cycles)</u> Only non-squamous: pemetrexed 500 mg/m^2 BSA IV, on day 1 of a 21-day cycle + cisplatin 75 mg/m^2 BSA IV or carboplatin AUC of 5 or 6 mg/mL/min, IV, day 1 of each 21-day cycle Non-squamous and squamous: gemcitabine 1250 mg/m² BSA, IV, on days 1 and 8 of a 21-week cycle + cisplatin 75 mg/m^2 BSA, IV, day 1 of a 21-day cycle, or carboplatin AUC of 5 or 6 mg/mL/min, IV, day 1 of a 21-day cycle or paclitaxel 200 mg/m^2 BSA, IV, on day 1 of a 21-day cycle + carboplatin AUC of 5 or 6 mg/mL/min, IV, day 1 of a 21-day cycle <u>Maintenance phase</u> Only non-squamous: after at least 4 cycles of carboplatin + pemetrexed, cisplatin + pemetrexed or paclitaxel + carboplatin, further treatment with pemetrexed 500 mg/m² BSA, IV, on day 1 of a 21-day cycle, was at the investigator's discretion

Table 7: Characteristics of the intervention – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Intervention	Comparison
KEYNOTE 024 (continued)	**Dose adjustments:** ▪ Pembrolizumab: no dose adjustment allowed (according to the SPC), interruption allowed in case of side effects ▪ Platinum-based chemotherapy: dose adjustments in accordance with the SPCs allowed	
	Permitted pretreatment ▪ Chemotherapy and/or radiotherapy as part of neoadjuvant or adjuvant treatment; the last treatment had to be administered at least 6 months prior to the diagnosis of the metastatic disease **Non-permitted pretreatment** ▪ systemic therapy for stage IV NSCLC ▪ CD137 agonists, anti-PD-1, anti-PD-L1, anti-PD-L2 and CTLA-4 therapeutic antibodies or immune checkpoint inhibitors **Non-permitted concomitant treatment** ▪ immunotherapies other than pembrolizumab ▪ other chemotherapies ▪ surgery for symptom and tumour control ▪ live vaccines ▪ corticosteroids except for the treatment of AEs or used as premedication of a platinum-based chemotherapy used in the study ▪ bisphosphonate or anti-RANKL inhibitors[e]	
KEYNOTE 042	Pembrolizumab 200 mg IV as 30-minute infusion on day 1 of a 21-day cycle	Carboplatin-based chemotherapy[a] for 4 to at most 6 cycles: Induction phase (4 to 6 cycles) Only non-squamous: pemetrexed 500 mg/m^2 BSA, IV, on day 1 of a 21-day cycle + carboplatin AUC of 5 or 6 mg/mL/min, IV, day 1 of a 21-day cycle Non-squamous and squamous: paclitaxel 200 mg/m^2 BSA, IV, on day 1 of a 21-day cycle + carboplatin AUC of 5 or 6 mg/mL/min, IV, day 1 of a 21-day cycle <u>Maintenance phase</u> Only non-squamous: after at least 4 cycles of platinum-based chemotherapy, further treatment with pemetrexed 500 mg/m² BSA, IV, on day 1 of a 21-day cycle, was at the investigator's discretion

Table 7: Characteristics of the intervention – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab (multipage table)

Study	Intervention	Comparison
KEYNOTE 042 (continued)	**Dose adjustments** ▪ Pembrolizumab: no dose adjustment allowed (treatment could be interrupted or discontinued) ▪ Chemotherapy: dose adjustments in accordance with the SPCs allowed	
	Pretreatment ▪ Adjuvant or neoadjuvant therapy; the last treatment had to be administered at least 6 months prior to the development of the metastatic disease **Non-permitted pretreatment** ▪ systemic therapy for the advanced or metastatic NSCLC stage ▪ CD137 agonists, anti-PD-1, anti-PD-L1, anti-PD-L2 and CTLA-4 therapeutic antibodies or immune checkpoint inhibitors **Non-permitted concomitant treatment** ▪ other chemotherapies or immunotherapies ▪ surgery for symptom or tumour control ▪ radiotherapy ▪ live vaccines ▪ corticosteroids except for the treatment of AEs or used as premedication of a chemotherapy used in the study	

a. The platinum-based chemotherapy was chosen by the investigator for the individual patients prior to randomization.
b. Treatment discontinuation was required for CTCAE grade ≥ 3 uveitis and for all non-haematological AEs with CTCAE grade 4.
c. Allowed as physiological replacement doses (also > 10 mg prednisone/day or equivalent), if not administered for immunosuppression.
d. Vitamin intake ≤ 3 days before randomization for patients with non-squamous NSCLC.
e. In the study, continuation of these therapies was only allowed for patients whose treatment had started prior to study inclusion.

AE: adverse event; AUC: area under the curve; BSA: body surface area; CD137: cluster of differentiation 137; CTCAE: Common Terminology Criteria for Adverse Events; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; RANKL: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial

Study design

Study with cemiplimab + platinum-based chemotherapy: EMPOWER-Lung 3

The EMPOWER-Lung 3 study is an ongoing, double-blind RCT comparing cemiplimab + platinum-based chemotherapy with placebo + platinum-based chemotherapy. The study included adult patients with histologically or cytologically confirmed locally advanced NSCLC (stage IIIB and IIIC) or metastatic NSCLC (stage IV). Patients with stage IIIB and IIIC disease were not allowed to be candidates for definitive chemoradiation, patients with stage IV disease were not allowed to have received prior systemic treatment for the advanced or metastatic stage. Furthermore, molecular genetic testing had to prove that the patients did

not have EGFR mutations, ALK translocations or ROS1 fusions. Good general health status at study entry, corresponding to an ECOG PS of 0 or 1, was also required for enrolment.

The EMPOWER-Lung 3 study included a total of 466 patients, allocated in a 2:1 ratio either to treatment with cemiplimab + platinum-based chemotherapy (N = 312) or placebo + platinum-based chemotherapy (N = 154). The treatment options of platinum-based chemotherapy were pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin, or paclitaxel + carboplatin. Treatment with pemetrexed was only an option for patients with non-squamous histology. The chemotherapy was chosen by the investigator prior to randomization and was based on the regional guidelines or standard health care. Randomization was stratified by histology (squamous versus non-squamous) and by PD-L1 expression (< 1% versus 1 to 49% versus ≥ 50%). The proportion of patients with squamous histology was limited to 50%. The proportion of patients with PD-L1 expression in < 1% of tumour cells was limited to 30%, with PD-L1 expression in < 50% of tumour cells to 70%, and with PD-L1 expression in ≥ 50% of tumour cells to 30 to 40%. PD-L1 expression of tumour tissue was determined using an immunohistochemical assay (SP263 Assay).

Administration of cemiplimab was in compliance with the specifications of the SPC [38]. Maximum treatment duration was 108 weeks. The combination of pemetrexed + cisplatin was applied in accordance with the specifications of the respective SPCs [39,40]. Neither the respective SPCs [39,41,42] nor the AM-RL on off-label use (Appendix VI to Section K [1]) contain information on the dosage of pemetrexed or paclitaxel, each in combination with carboplatin. Deviating from the SPC [40,42], paclitaxel in combination with cisplatin was administered at a dosage of 200 mg/m² body surface area (BSA) paclitaxel instead of 175 mg/m² BSA, followed by cisplatin at a dosage of 75 mg/m² BSA instead of 80 mg/m² BSA. The platinum-based chemotherapies were applied on day 1 of each 21-day treatment cycle over a period of 4 cycles. In the case of therapy with pemetrexed + cisplatin or carboplatin for non-squamous NSCLC histology, further treatment with pemetrexed is mandatory after the induction phase of 4 cycles.

Treatment was until disease progression, death, unacceptable toxicity, initiation of subsequent antineoplastic therapy or withdrawal of consent. After confirmed progression in the cemiplimab arm before reaching the 108th week of treatment, patients with eligibility confirmed by the investigator could continue treatment with cemiplimab. For patients with confirmed disease progression in the comparator arm, study treatment was stopped. Switching to treatment in the intervention arm was not possible.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and AEs.

Data cut-offs

The following data cut-offs are available for the EMPOWER-Lung 3 study.

- First data cut-off on 3 January 2021: The first prespecified interim analysis was planned after the occurrence of 146 (50%) deaths in the total study population.
- Second data cut-off on 14 June 2021: The second prespecified interim analysis (primary analysis) was planned after the occurrence of 204 (70%) deaths in the total study population.
- Third data cut-off on 14 June 2022: This was a post hoc data cut-off. The analyses were updated to the therapeutic indication approved by the European Medicines Agency (EMA) (patients with a PD-L1 expression of the tumour cells of ≥ 1%). The results of this data cut-off are presented in the European Public Assessment Report (EPAR).

Results of the EMPOWER-Lung 3 study presented by the company

The company presented only results on the 14 June 2022 data cut-off for 2 subpopulations. On the one hand, these were the results of patients with PD-L1 expression of tumour cells of ≥ 50% and non-squamous histology who were assigned to treatment with pemetrexed + carboplatin or cisplatin before randomization (48 in the intervention arm versus 21 in the comparator arm); on the other, the results of patients with PD-L1 expression of tumour cells of ≥ 50% and squamous histology who were assigned to treatment with paclitaxel + carboplatin before randomization (35 in the intervention arm versus 21 in the comparator arm). The company only presented results for the outcome of overall survival; information on other outcomes in the categories of morbidity, health-related quality of life and side effects is missing, as are the results for the prespecified data cut-off from 14 June 2021.

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

As already described in the dossier assessments on the projects A17-06, A19-30 and A21-98, KEYNOTE 024 is a completed, open-label RCT on the comparison of pembrolizumab with a platinum-based chemotherapy. The study included adult patients with histologically or cytologically confirmed metastatic NSCLC without EGFR mutation or ALK translocation, whose tumours had PD-L1 expression ≥ 50%. The patients had to be in good general condition (according to an ECOG PS ≤ 1). Prior systemic antineoplastic treatment for the metastatic stage was not allowed.

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based chemotherapy (N = 151). The treatment options were as follows: pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine +

carboplatin, or paclitaxel + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous histology. The treatment suitable for each patient was specified by an investigator on an individual basis prior to randomization. Randomization was stratified by histology (squamous, non-squamous), geographical region (East Asia, not East Asia) and ECOG PS (0, 1).

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 Assay. Pembrolizumab was administered in accordance with the SPC [43]. The maximum treatment duration for pembrolizumab was 35 cycles (105 weeks). The platinum-based chemotherapies (pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin) were also administered in accordance with the respective SPCs [39-42,44]. Neither the respective SPCs [41,42] nor the AM-RL on off-label use (Appendix VI to Section K [1]) contained information on the dosage of paclitaxel in combination with carboplatin. The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the KEYNOTE 024 study. Thereafter, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended.

Patients were treated disease until progression, unacceptable side effects, or study discontinuation upon the investigator's or patient's discretion. After disease progression, suitable patients in the comparator arm could switch to monotherapy with pembrolizumab. The approval of pembrolizumab specifies this treatment option after prior chemotherapy. There were no further specifications regarding subsequent therapies.

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

Results of the KEYNOTE 024 study presented by the company

In its dossier, the company presented the results of a subpopulation of the KEYNOTE 024 study at the 9 May 2016 data cut-off. This is the second interim analysis, which was also used in the previous projects A19-30 and A21-98. The subpopulation includes patients with non-squamous histology, PD-L1 expression in ≥ 50% of the tumour cells, and a chemotherapy regimen consisting of carboplatin + pemetrexed or cisplatin + pemetrexed. The company used analyses available from the benefit assessment procedure 2019-04-01-D-447 for this subpopulation. These analyses are limited to patients for whom, according to a retrospective investigator survey carried out by the company for the procedures of the time, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL for the off-label use (Appendix VI to Section K [1]). In this survey, several criteria were used to assess whether carboplatin was a more suitable treatment option than cisplatin. These included safety or efficacy concerns with cisplatin, contraindications due to existing comorbidities (e.g.

tinnitus, renal insufficiency and neuropathies) and the toxicity profile of the 2 substances. Patients who had been treated with carboplatin based on these criteria were included in the subpopulation called TPC population. This retrospective restriction of the study population means that 50 of 116 (43%) patients in the intervention and comparator arm who were assigned to therapy with carboplatin are not included in the analysis. The company used the TPC subpopulation for the benefit assessment. In its dossier, the company only presented the results for the outcome of overall survival.

KEYNOTE 042

As already described in the dossier assessments on the projects A19-30, A19-31 and A21-98, KEYNOTE 042 is a completed, open-label RCT. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. The study included adults with histologically or cytologically confirmed diagnosis of NSCLC whose tumours expressed PD-L1 ≥ 1% and who were in the locally advanced or metastatic stage. Prior systemic treatment was not allowed in the study. For patients who had received adjuvant or neoadjuvant therapy, this treatment had to be completed 6 months prior to the development of metastases. Included patients had to have an ECOG PS of 0 or 1. Prior to randomization, an investigator decided which treatment option (pemetrexed + carboplatin or paclitaxel + carboplatin) would be suitable for each individual patient in the event of randomization to the comparator arm; however, the combination with pemetrexed was only an option for patients with non-squamous histology.

A total of 1274 patients were randomized in a 1:1 ratio either to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637). Randomization was stratified by ECOG PS (0, 1), histology (squamous, non-squamous), PD-L1 expression (≥ 50%, 1 to 49%) and geographical region (East Asia, not East Asia). In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 Assay.

Patients in the intervention arm received pembrolizumab in accordance with the requirements of the SPC [43]. The maximum treatment duration was 35 cycles (105 weeks). The platinum-based chemotherapy of pemetrexed + carboplatin was also administered in accordance with the requirements of the SPC [39,41,42]. Neither the respective SPCs [41,42] nor the AM-RL on off-label use (Appendix VI to Section K [1]) contained information on the dosage of paclitaxel in combination with carboplatin. In the KEYNOTE 042 study, patients with non-squamous histology received carboplatin for a maximum of 4 to 6 cycles. After at least 4 cycles, maintenance treatment with pemetrexed was possible and recommended for patients with non-squamous histology.

Patients were treated until disease progression, complete response, unacceptable side effects, or study discontinuation upon the investigator’s or patient’s discretion.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could receive subsequent therapies. There were no limitations regarding the type of subsequent therapy. The study design did not explicitly intend a switch of treatment from the ACT to pembrolizumab monotherapy after disease progression.

The study's primary outcome was overall survival. Patient-relevant secondary outcomes were AEs.

Results of the KEYNOTE 042 study presented by the company

In its dossier, the company presented analyses of 2 subpopulations of the KEYNOTE 042 study at the 26 February 2018 data cut-off. This is the second interim analysis, which was also used in the previous projects A19-30, A19-31 and A21-98. On the one hand, these 2 subpopulations include patients with non-squamous histology, PD-L1 expression in ≥ 50% of tumour cells, and a chemotherapy regimen consisting of carboplatin + pemetrexed; on the other, patients with squamous histology, PD-L1 expression in ≥ 50% of tumour cells, and a chemotherapy regimen consisting of carboplatin + paclitaxel. These analyses from the benefit assessment procedures 2019-04-01-D-447 + 2019-04-01-D-448 are available, but are limited to those patients for whom, according to a retrospective investigator survey carried out by the company for the procedures of the time, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL for the off-label use (Appendix VI to Section K [1]). The subpopulations are each referred to as "TPC population" (see also the KEYNOTE 024 study). This procedure means that 123 of 299 (41%) patients in the intervention and comparator arm with non-squamous NSCLC histology who were assigned to therapy with carboplatin are not included in the analysis. In the case of patients with squamous histology, this limitation affects 61 out of 181 (34%) patients. The company used the TPC populations for the benefit assessment. In its dossier, the company only presented the results for the outcome of overall survival.

Patient characteristics presented cannot be meaningfully interpreted

In Module 4 E, the company presented the patient characteristics for the EMPOWER-Lung 3 study for the subpopulation of patients with a PD-L1 expression of the tumour cells of ≥ 50% separately according to squamous (N = 56) and non-squamous (N = 69) histology. For the KEYNOTE 024 and KEYNOTE 042 studies, the company's Module 4 E presented patient characteristics of the post-hoc restricted subpopulations, which only included patients suitable for treatment with carboplatin according to the investigator's assessment. These different operationalizations for the formation of the subpopulations in the EMPOWER-Lung 3 study compared with the KEYNOTE studies mean that the subpopulations presented by the company do not have the similarity required for an indirect comparison. Therefore, a meaningful interpretation of the patient characteristics presented is not possible.

Information on treatment duration and observation period is incomplete or missing

Information on treatment duration is only available for the EMPOWER-Lung 3 study. Information on the observation period is completely missing for all studies.

Therefore, it is not possible to assess the similarity of the studies with regard to the patients' treatment durations and observation periods.

Information on subsequent therapies is missing

Information on subsequent therapies is missing in Module 4 E for both the EMPOWER-Lung 3 study and the KEYNOTE 024 and KEYNOTE 042 studies.

Therefore, it is not possible to assess the similarity of the studies with regard to the patients' subsequent therapies.

I 3.1.3 Similarity of the studies for the indirect comparison

In the following, key aspects that affect the similarity of the studies for conducting an adjusted indirect comparison are discussed beyond the study characteristics described in Section I 3.1.2.

Similarity of the study populations

In principle, the 3 studies EMPOWER-Lung 3, KEYNOTE 024 and KEYNOTE 042 have a similar study design. For the present adjusted indirect comparisons, the company chose platinum-based chemotherapy as common comparator. Different chemotherapy regimens were possible in the 3 included studies EMPOWER-Lung 3, KEYNOTE 024 and KEYNOTE 042 (see also Table 7). To enable an indirect comparison, the company therefore limited these regimens to individual treatment options. For patients with non-squamous NSCLC histology, the company used those subpopulations from the EMPOWER-Lung 3, KEYNOTE-024 and 042 studies whose platinum-based chemotherapy consisted of pemetrexed + carboplatin or pemetrexed + cisplatin. For patients with squamous NSCLC histology, the company restricted the subpopulations of the EMPOWER-Lung 3 and KEYNOTE 042 studies based on the carboplatin + paclitaxel chemotherapy regimen specified by the company. To form the corresponding subpopulations from both KEYNOTE studies, the company additionally only used the results of those patients for whom, according to a retrospective survey, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K [1]) (see Table 6). The previously described post-hoc limitations based on the chemotherapy regimen and retrospective survey on carboplatin result in relevant proportions of the study populations of the KEYNOTE studies not being included in the analyses. This leads, for example, to 43% of patients in the KEYNOTE 024 study not being included in the analysis. In the EMPOWER-Lung 3 study, the company did not make such a post-hoc restriction of the populations based on the use of carboplatin in accordance with the

AM-RL on off-label use (Appendix VI to Section K [1]). Thus, it can be assumed that the presented subpopulations of the KEYNOTE 024 and KEYNOTE 042 studies differ to a relevant extent from the subpopulation of the EMPOWER-Lung 3 study.

Usability of the indirect comparisons presented by the company

A key prerequisite for the consideration of studies in the adjusted indirect comparison is similarity with regard to study design, intervention, common comparator, patient characteristics, treatment duration, observation period, and subsequent therapies, among others. The patient characteristics presented by the company in Module 4 E cannot be meaningfully interpreted, as the subpopulations formed do not have the similarity required for an indirect comparison. The information on treatment duration and observation period, on subsequent therapies and on the distribution of the platinum component for the presented subpopulations of the EMPOWER-Lung 3 study and the KEYNOTE 024 and KEYNOTE 042 studies is incomplete or missing entirely.

In particular, it can be assumed that there is a relevant difference between the subpopulations of the KEYNOTE 024 and KEYNOTE 042 studies and the subpopulation of the EMPOWER-Lung 3 study due to the post-hoc restriction to those patients for whom, according to a retrospective survey, carboplatin was a suitable treatment option in accordance with the AM-RL on off-label use (Appendix VI to Section K [1]).

Furthermore, although the company presented results for the outcome categories of mortality, morbidity, health-related quality of life and side effects for the total population of the EMPOWER-Lung 3 study, it only provided information on the outcome of overall survival for the subpopulations of patients with a PD-L1 expression of the tumour cells of ≥ 50% and non-squamous histology or squamous histology it had formed, and only used this outcome for the indirect comparisons. It justified the latter with the fact that all outcomes except overall survival in the KEYNOTE 024 and KEYNOTE 042 studies were to be regarded as potentially highly biased due to the open-label study design and therefore could not be used to derive the added benefit within the framework of an adjusted indirect comparison. This justification is not appropriate. The results of the patient-relevant outcomes in the indirect comparison are required to be able to make an appropriate balancing of benefit and harm. The risk of bias and the associated interpretability of the results are assessed for each outcome. For this reason alone, no sufficient data is available for balancing benefit and harm.

I 3.2 Results on added benefit

The data presented by the company for the assessment of the added benefit of cemiplimab + platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or with metastatic NSCLC expressing PD-L1 in ≥ 50% of tumour cells, with no EGFR, ALK or ROS1 aberrations, are

not suitable for deriving an added benefit of cemiplimab + platinum-based chemotherapy compared with the ACT. This results in no hint of added benefit of cemiplimab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

The data presented by the company for the assessment of the added benefit of cemiplimab + platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or with metastatic NSCLC expressing PD-L1 in ≥ 50% of tumour cells, with no EGFR, ALK or ROS1 aberrations, are not suitable for deriving an added benefit of cemiplimab + platinum-based chemotherapy compared with the ACT. An added benefit of cemiplimab + platinum-based chemotherapy for these patients is therefore not proven.

The assessment described above deviates from that of the company, which derived a non-quantifiable added benefit in comparison with pembrolizumab as ACT for all patients in the newly approved therapeutic indication of cemiplimab + platinum-based chemotherapy – regardless of PD-L1 expression and NSCLC histology.

I 4 Research question 2: patients with PD-L1 expression of tumour cells from 1 to 49%

I 4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on cemiplimab (status: 15 February 2023)
- bibliographical literature search on cemiplimab (last search on 15 February 2023)
- search in trial registries/trial results databases for studies on cemiplimab (last search on 15 February 2023)
- search on the G-BA website for cemiplimab (last search on 15 February 2023)
- bibliographical literature search on the ACT (last search on 15 February 2023)
- search in trial registries/trial results databases for studies on the ACT (last search on 15 February 2023)
- search on the G-BA website for the ACT (last search on 15 February 2023)

To check the completeness of the study pool:

- search in trial registries for studies on cemiplimab (last search on 3 May 2023); for search strategies, see I Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 4 May 2023); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company's findings, the check of completeness of the study pool did not identify any study for a direct comparison of cemiplimab with the ACT.

The company therefore presented 2 adjusted indirect comparisons according to Bucher [4] for the assessment of cemiplimab + platinum-based chemotherapy compared with pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1 and non-squamous histology), or pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG PS 0–1 and squamous histology) using platinum-based chemotherapy as common comparator. In the following, the 2 comparator therapies selected by the company are referred to with the simplified term "pembrolizumab + platinum-based chemotherapy".

The company justified the choice of the common comparator by stating that the identified EMPOWER-Lung 3 study with the drug to be assessed (cemiplimab + platinum-based chemotherapy versus platinum-based chemotherapy) was the only RCT in the relevant

therapeutic indication, and that therefore a comparison with the ACT specified by the G-BA (pembrolizumab + platinum-based chemotherapy) was only possible with a platinum-based chemotherapy as common comparator. The choice of the common comparator is appropriate.

The check of the study pool did not identify any additional relevant study for the adjusted indirect comparison presented by the company.

I 4.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 8: Study pool – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Cemiplimab + platinum-based chemotherapy vs. platinum-based chemotherapy						
EMPOWER-Lung 3[d] (R2810-ONC-16113)	Yes	Yes	No	Yes [5]	Yes [6,7]	Yes [8-11]
Pembrolizumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
KEYNOTE 189	No	No	Yes	No	Yes [45,46]	Yes [22-24,47-50]
KEYNOTE 189-Japan	No	No	Yes	No	Yes [51]	Yes [52]
KEYNOTE 021G	No	No	Yes	No	Yes [53]	Yes [54,55]
KEYNOTE 407	No	No	Yes	No	Yes [56,57]	Yes [33-35,58-61]
KEYNOTE 407-China	No	No	Yes	No	Yes [62]	Yes [63]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this designation.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool concurs with that of the company.

The company's study pool comprised the RCT EMPOWER-Lung 3 for cemiplimab + platinum-based chemotherapy, and the RCTs KEYNOTE 189, KEYNOTE 189-Japan, KEYNOTE 021G, KEYNOTE 407 and KEYNOTE 407-China for pembrolizumab + platinum-based chemotherapy.

The extension studies KEYNOTE 189-Japan and KEYNOTE 407-China were conducted according to the same study protocol as the studies KEYNOTE 189 and KEYNOTE 407 . The company did not use the studies KEYNOTE 189-Japan and KEYNOTE 407-China for the indirect comparisons, as the data of the extension studies are not available in a comparably processed form as for the studies KEYNOTE 189 and KEYNOTE 407. Also for the KEYNOTE 021G study, no data are available for the relevant subpopulation (PD-L1 expression of tumour cells from 1 to 49%). As a result, there is a lack of data on patient characteristics, chemotherapy regimens, treatment durations, observation periods, and results for the relevant subpopulation, for example. Sufficient similarity of the patient populations in the studies in the indirect comparison is one of the prerequisites for a consideration of the studies in the indirect comparison. The similarity cannot be tested without information on the relevant subpopulation. The non-consideration of the studies KEYNOTE 189-Japan, KEYNOTE 021G and KEYNOTE 407-China is appropriate.

Figure 4 shows a schematic representation of the adjusted indirect comparison.

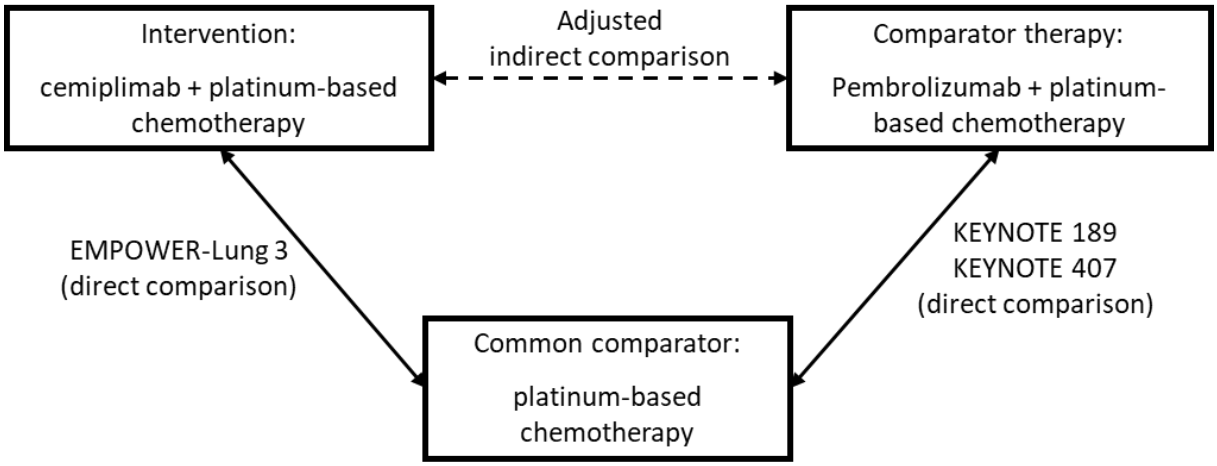

Figure 4: Study pool for the adjusted indirect comparison between cemiplimab + platinum-based chemotherapy and pembrolizumab + platinum-based chemotherapy using platinum-based chemotherapy as the common comparator (patients with a PD-L1 expression of tumour cells from 1 to 49%)

Indirect comparisons presented by the company

Since the KEYNOTE 189 study only included patients with non-squamous NSCLC and the KEYNOTE 407 study only included patients with squamous NSCLC, the company subdivided the population of research question 2 (patients with PD-L1 expression of the tumour cells from 1 to 49%) into 2 subpopulations based on NSCLC histology:

- Patients with a PD-L1 expression of the tumour cells from 1 to 49% and non-squamous NSCLC

- Patients with a PD-L1 expression of the tumour cells from 1 to 49% and squamous NSCLC

However, the company did not give any consideration to combining the results of the 2 indirect comparisons in accordance with the G-BA's research question.

For the adjusted indirect comparison of patients with non-squamous NSCLC, the company used a subpopulation of the EMPOWER-Lung 3 study and the KEYNOTE 189 study. Figure 5 shows a schematic representation of the adjusted indirect comparison.

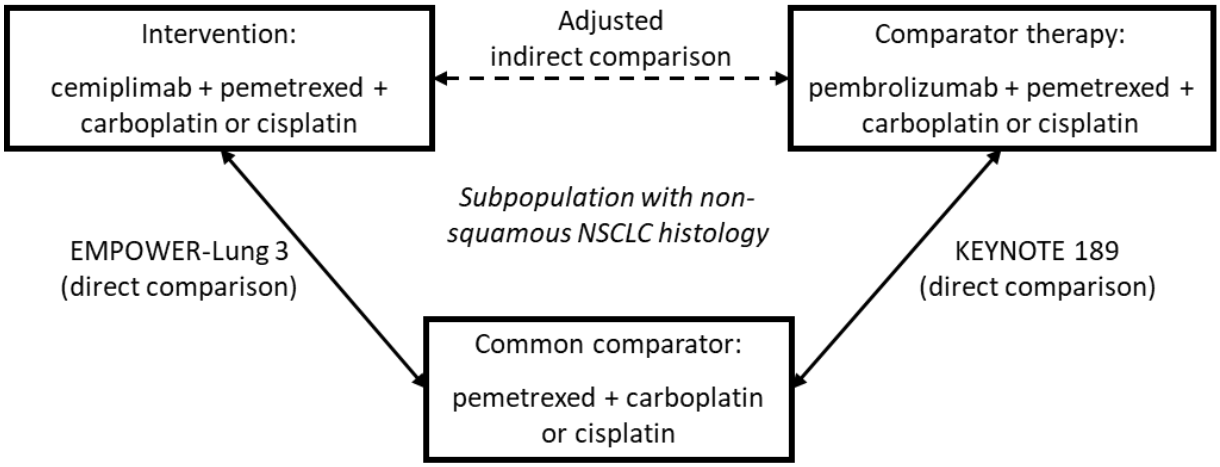

Figure 5: Study pool for the indirect comparison between cemiplimab + platinum-based chemotherapy and pembrolizumab + platinum-based chemotherapy using platinum-based chemotherapy as the common comparator (patients with non-squamous NSCLC histology)

For the adjusted indirect comparison of patients with squamous NSCLC, the company used a subpopulation of the EMPOWER-Lung 3 study and the KEYNOTE 407 study. Figure 6 shows a schematic representation of the adjusted indirect comparison.

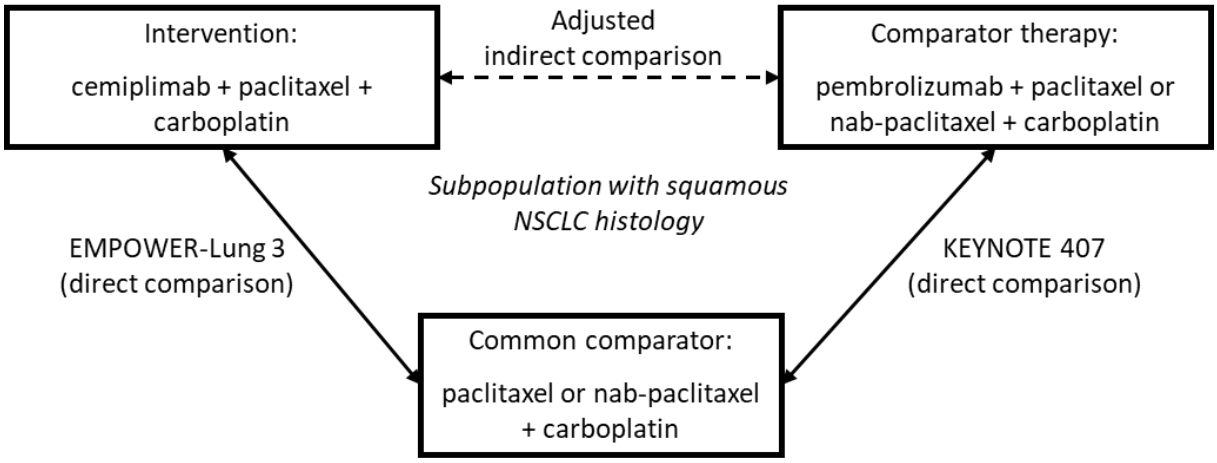

Figure 6: Study pool for the indirect comparison between cemiplimab + platinum-based chemotherapy and pembrolizumab + platinum-based chemotherapy using platinum-based chemotherapy as the common comparator (patients with squamous NSCLC histology)

The company presented results of the indirect comparisons only for the outcome of overall survival

The company only presented results for the outcome of overall survival for both indirect comparisons. Results for the outcome categories of morbidity, health-related quality of life and side effects are not available in Module 4 E. The company justified its approach by stating that no data were available for further outcomes for the subpopulation (PD-L1 expression of tumour cells from 1 to 49%) of the KEYNOTE 189 and KEYNOTE 407 studies. For this reason alone, no sufficient data is available for balancing benefit and harm.

Similarity of the study population is not given, and analyses presented by the company are not usable for the indirect comparison

The similarity of the study populations required for an indirect comparison is not given. The main reason for this is that the company used a retrospectively restricted subpopulation of the KEYNOTE 189 and KEYNOTE 407 studies from previous benefit assessment procedures. Due to this restriction, only those patients were considered for whom carboplatin was a suitable treatment option in accordance with the AM-RL on off-label use (Appendix VI to Section K [1]). Another decisive aspect is that the subpopulations of the KEYNOTE 189 and KEYNOTE 407 studies used for the assessment include a relevant number of patients who are not comprised by the research question (see below). Overall, it can be assumed that there is a relevant difference between the relevant subpopulation of the EMPOWER-Lung 3 study and the presented subpopulations of the KEYNOTE 189 and KEYNOTE 407 studies. In addition, further aspects cannot be assessed with sufficient certainty for the evaluation of the similarity of the studies due to missing data (treatment duration and observation period as well as subsequent therapies) (see Section I 4.1.2).

The analyses presented by the company cannot be used for the benefit assessment. This is explained below.

I 4.1.2 Study characteristics

Table 9 and Table 10 describe the studies used for the benefit assessment.

Table 9: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Cemiplimab + platinum-based chemotherapy vs. platinum-based chemotherapy						
EMPOWER-Lung 3	RCT, double-blind, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed NSCLC, squamous or non-squamous, without EGFR mutation, ALK or ROS1 translocation, ECOG PS ≤ 1 ▪ stage IIIB or IIIC and not candidates for definitive chemoradiation, or ▪ stage IV, without previous systemic therapy[b, c]	Cemiplimab + platinum-based chemotherapy[d] (N = 312) Placebo + platinum-based chemotherapy[d] (N = 154) <u>Subpopulation thereof analysed by the company[e]:</u> ▪ PD-L1 expression 1 to 49%, non-squamous ▫ Cemiplimab + pemetrexed + carboplatin or cisplatin (n = 53) ▫ Placebo + pemetrexed + carboplatin or cisplatin (n = 22) ▪ PD-L1 expression 1 to 49%, squamous ▫ Cemiplimab + paclitaxel + carboplatin (n = 49) ▫ Placebo + paclitaxel + carboplatin (n = 23)	Screening: 28 days before randomization Treatment: until progression, death, withdrawal of consent, unacceptable toxicity, initiation of other subsequent antineoplastic therapy, or after a maximum of 108 weeks of cemiplimab or placebo Observation: outcome-specific, at most until death (for the outcome of overall survival)	74 centres in: China, Georgia, Greece, Malaysia, Poland, Romania, Russia, Thailand, Turkey, Ukraine 31 May 2019–ongoing Data cut-offs: 3 January 2021[f] 14 June 2021[g] 14 June 2022[h]	Primary: overall survival Secondary: morbidity, health-related quality of life, AEs

Table 9: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Pembrolizumab + platinum-based chemotherapy vs. platinum-based chemotherapy						
KEYNOTE 189	RCT, double-blind, parallel	Adults (≥ 18 years) with histologically or cytologically confirmed stage IV non-squamous NSCLC without EGFR mutation or ALK translocation and ECOG PS ≤ 1, without previous systemic therapy[b, c]	▪ Pembrolizumab + platinum-based chemotherapy (N = 410) ▪ platinum-based chemotherapy (N = 206) Subpopulation thereof presented by the company (TPC survey population)[e, i]: ▪ PD-L1 expression < 50%, non-squamous ▫ Pembrolizumab + pemetrexed + carboplatin or cisplatin (n = 162) ▫ pemetrexed + carboplatin or cisplatin (n = 88)	Screening: up to 28 days before start of treatment Treatment: until progression, unacceptable side effects, investigator's or patient's decision, complete response, or a maximum of 35 cycles of pembrolizumab[j] Observation: outcome-specific, at most until death (for the outcome of overall survival)	143 centres in: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Spain, United Kingdom, USA 2/2016–ongoing Data cut-off: 8 November 2017 (prespecified, first interim analysis) Final analysis planned after about 416 deaths	Primary: PFS, overall survival Secondary: morbidity, health-related quality of life, AEs

Table 9: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE 407	RCT, double-blind, parallel	Adults with histologically or cytologically confirmed stage IV squamous NSCLC, ECOG ≤ 1 and without previous systemic therapy[b, c]	▪ Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (n = 278) ▪ Carboplatin and either paclitaxel or nab-paclitaxel (N = 281) Subpopulation thereof presented by the company (TPC survey population)[e, i]: ▪ PD-L1 expression < 50%, squamous ▫ Pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel (n = 157) ▫ Carboplatin + paclitaxel or nab-paclitaxel (n = 153)	Screening: 28 days prior to the start of treatment Treatment: Until complete response or until progression, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, pregnancy, treatment discontinuation upon the physician's or patient's discretion or after a maximum of 35 cycles of pembrolizumab[j] Follow-up: at most until death	125 centres in Australia, Canada, China, Germany, France, Hungary, Italy, Japan, Mexico, Netherlands, Poland, Russia, South Korea, Spain, Thailand, Turkey, and United States 8/2016–ongoing Data cut-off: 3 April 2018 (prespecified, second interim analysis) Final analysis planned after about 361 deaths	Primary: overall survival, PFS Secondary: morbidity, health-related quality of life, AEs

Table 9: Characteristics of the studies included – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on outcomes relevant for this benefit assessment.
b. For patients who had received neoadjuvant or adjuvant treatment, the last treatment had to be completed at least 6 months (EMPOWER-Lung 3) or 12 months (KEYNOTE 189 and KEYNOTE 407) prior to the diagnosis of the metastatic disease.
c. Without prior systemic therapy for the NSCLC stage IIIB and IV (KEYNOTE 189 und KEYNOTE 407) or the advanced or metastatic NSCLC stage (EMPOWER-Lung 3).
d. Prior to randomization, a choice for the individual patient was made at the investigator's discretion, according to the local standard of care, between the following platinum-based chemotherapies: pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin, paclitaxel + carboplatin. Combinations with pemetrexed were only allowed for patients with non-squamous histology.
e. For the adjusted indirect comparison in non-squamous histology, only patients were considered who had been assigned to platinum-based chemotherapy consisting of carboplatin + pemetrexed or cisplatin + pemetrexed (KEYNOTE 189) prior to randomization. For the adjusted indirect comparison in squamous histology, only patients were considered who had been assigned to platinum-based chemotherapy consisting of carboplatin + paclitaxel or nab-paclitaxel (KEYNOTE 407) prior to randomization.
f. First planned interim analysis after about 146 deaths (50%).
g. Second planned interim analysis after about 204 deaths (70%), primary analysis.
h. 2 post-hoc analyses were conducted on this data cut-off. With the second post-hoc analysis, the primary analysis was updated to the therapeutic indication approved by the EMA and thus restricted to patients with a PD-L1 expression of the tumour cells of ≥ 1%.
i. The subpopulation comprises patients who, according to the results of the TPC survey by the company, were treated in accordance with the criteria of the AM-RL for the off-label use (Appendix VI to Section K [1]) of carboplatin and have a PD-L1 expression in ≤ 50% of tumour cells.
j. Patients in the intervention arm (KEYNOTE 407) or in both arms (KEYNOTE 189) could temporarily discontinue treatment after confirmed complete response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab at the investigator's discretion after subsequent confirmed progression (if certain conditions regarding previous treatment duration and disease status were met) ("second course phase"). Based on the study documents it can be assumed that no patient (KEYNOTE 189) reached the "second course phase".

AE: adverse event; ALK: anaplastic lymphoma kinase; AM-RL: Pharmaceutical Directive; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EMA: European Medicines Agency; n: subpopulation analysed and presented by the company; N: number of randomized patients; nab: albumin-bound nanoparticles; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; ROS1: c-ros oncogene 1; TPC: treatment of physician's choice

Table 10: Characteristics of the intervention – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy (multipage table)

Study	Intervention	Comparison
Cemiplimab + platinum-based chemotherapy vs. platinum-based chemotherapy		
EMPOWER-Lung 3	See information in Table 7	
Pembrolizumab + platinum-based chemotherapy vs. platinum-based chemotherapy		
KEYNOTE 189	Pembrolizumab 200 mg IV (as 30-minute infusion) every 3 weeks for a maximum of 35 cycles + platinum-based chemotherapy[a]: ▪ cisplatin 75 mg/m² BSA IV (approx. 30 minutes following pemetrexed infusion) every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² BSA IV (as 10-minute infusion) every 3 weeks or ▪ carboplatin AUC 5 mg/mL/min (750 mg max) IV (as 15 to 60-minute infusion), every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² BSA IV (as 10-minute infusion) every 3 weeks	Placebo for pembrolizumab (as 30-minute infusion) every 3 weeks for a maximum of 35 cycles + platinum-based chemotherapy[a]: ▪ cisplatin 75 mg/m² BSA IV (approx. 30 minutes following pemetrexed infusion) every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² BSA IV (as 10-minute infusion) every 3 weeks or ▪ carboplatin AUC 5 mg/mL/min (750 mg max) IV (as 15 to 60-minute infusion), every 3 weeks for 4 cycles + ▪ pemetrexed 500 mg/m² BSA IV (as 10-minute infusion) every 3 weeks
	Dose adjustments in case of toxicities ▪ Pembrolizumab: no dose adjustment allowed (treatment could be interrupted or discontinued) ▪ Platinum-based chemotherapy: dose adjustments in accordance with the protocol allowed	
	Pretreatment ▪ Patients who had received previous adjuvant or neoadjuvant therapy could participate in the study, provided that the treatment had been completed ≥ 12 month prior to diagnosis of the metastatic disease **Non-permitted pretreatment** ▪ systemic treatment of stage IV NSCLC **Non-permitted concomitant treatment** ▪ other systemic chemotherapies or biologic treatments ▪ other chemotherapies or immunotherapies ▪ radiotherapies ▪ live vaccines ▪ corticosteroids (> 7 days) except for the treatment of AEs or used as premedication of a platinum-based chemotherapy used in the study ▪ phenytoin (during cisplatin/carboplatin)	

Table 10: Characteristics of the intervention – RCT, indirect comparison: cemiplimab + platinum-based chemotherapy vs. pembrolizumab + platinum-based chemotherapy (multipage table)

Study	Intervention	Comparison
KEYNOTE 407	Pembrolizumab 200 mg IV as 30-minute infusion every 3 weeks for a maximum of 35 cycles + carboplatin-based chemotherapy[a] for 4 cycles: ▪ carboplatin AUC 6 mg/mL/min (900 mg max) IV as 15 to 60-minute infusion on day 1 of the 3-week-cycle + ▪ paclitaxel 200 mg/m² BSA IV as 3-hour infusion on day 1 of the 3-week cycle or ▪ nab-paclitaxel 100 mg/m² BSA IV as 30-minute infusion on days 1, 8 and 15 of the 3-week cycle	placebo solution IV as 30-minute infusion every 3 weeks for a maximum of 35 cycles + carboplatin-based chemotherapy[a] for 4 cycles: ▪ carboplatin AUC 6 mg/mL/min (900 mg max) IV as 15 to 60-minute infusion on day 1 of the 3-week-cycle + ▪ paclitaxel 200 mg/m² BSA IV as 3-hour infusion on day 1 of the 3-week cycle or ▪ nab-paclitaxel 100 mg/m² BSA IV as 30-minute infusion on days 1, 8 and 15 of the 3-week cycle
	Dose adjustments in case of toxicities ▪ Pembrolizumab: no dose adjustment allowed (treatment could be interrupted or discontinued) ▪ Platinum-based chemotherapy: dose adjustments in accordance with the protocol allowed	
	Pretreatment ▪ Adjuvant or neoadjuvant therapy; the last treatment had to be administered at least 12 months prior to the development of the metastatic disease **Non-permitted pretreatment** ▪ systemic treatment of stage IIIB and IV NSCLC **Non-permitted concomitant treatment** ▪ other antineoplastic systemic chemotherapy or biologic treatments ▪ other chemotherapies or immunotherapies ▪ systemic corticosteroids (> 7 days of treatment) except for the treatment of AEs or used as premedication of a chemotherapy used in the study ▪ radiotherapy ▪ live vaccines	

a. In the framework of the chemotherapy, a platinum-based chemotherapy was chosen by the investigator for the individual patients prior to randomization.

AUC: area under the curve; BSA: body surface area; CTCAE: Common Terminology Criteria for Adverse Events; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; nab: albumin-bound nanoparticles; NSCLC: non-small cell lung cancer; PD-1: programmed cell death protein-1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

Study design

Study with cemiplimab + platinum-based chemotherapy: EMPOWER-Lung 3

Since the company used the EMPOWER-Lung 3 study also to assess the added benefit in patients with PD-L1 expression of the tumour cells of ≥ 50%, the description of the study can be found in Section I 3.1.2.

Subpopulation (patients with a PD-L1 expression of the tumour cells from 1 to 49%) of the EMPOWER-Lung 3 study presented by the company

According to the approval of cemiplimab + platinum-based chemotherapy, first-line treatment is limited to adult patients with NSCLC expressing PD-L1 in ≥ 1% of tumour cells [38]. For the EMPOWER-Lung 3 study, the company therefore presented data of the subpopulation of patients with PD-L1 expression of the tumour cells from 1 to 49%. To ensure better comparability, the company additionally restricted the patient population for the adjusted indirect comparison with regard to the chemotherapy regimens administered. For this purpose, in the case of non-squamous histology, it only considered patients who had been assigned to a chemotherapy combination of pemetrexed and carboplatin or cisplatin before randomization, and in the case of squamous histology, it only considered patients who had been assigned to a chemotherapy combination of paclitaxel and carboplatin before randomization.

The subpopulation with non-squamous NSCLC histology thus comprises 53 patients in the intervention arm versus 22 in the comparator arm; and the subpopulation with squamous NSCLC histology comprises 49 patients in the intervention arm versus 23 in the comparator arm.

Overall, in addition to the patient characteristics, the company only presented the result of the primary outcome of overall survival for the subpopulations, however. Results for the outcome categories of morbidity, health-related quality of life and side effects are not available in Module 4 E. The company justified its approach by stating that no data were available for further outcomes for the subpopulation (PD-L1 expression of tumour cells from 1 to 49%) of the KEYNOTE 189 and KEYNOTE 407 studies.

Studies with the ACT: KEYNOTE 189 and KEYNOTE 407

Study KEYNOTE 189

As already described in the dossier assessment on project A19-30, KEYNOTE 189 is an ongoing RCT on the comparison of pembrolizumab + platinum-based chemotherapy with a platinum-based chemotherapy. The study included adults with histologically or cytologically confirmed stage IV non-squamous NSCLC without EGFR mutation or ALK translocation and ECOG PS ≤ 1 irrespective of the PD-L1 expression. Prior systemic treatment against stage IV NSCLC was not allowed.

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 Assay.

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

The administration of pembrolizumab concurred with the requirements of the SPC [43]. The maximum treatment duration for pembrolizumab was 35 cycles. The platinum-based chemotherapies were administered in compliance with the respective SPCs [39-41] or the AM-RL on off-label use (Appendix VI to Section K [1]). The platinum component of the platinum-based chemotherapy was administered for a maximum of 4 cycles in both studies. After the initial 4 cycles, pemetrexed was continued at 3-week intervals.

Patients were treated until disease progression, unacceptable side effects, or treatment discontinuation upon the investigator's or patient's discretion. After disease progression, suitable patients in the comparator arm could switch to monotherapy with pembrolizumab. There were no further specifications regarding subsequent therapies.

The primary outcomes of the KEYNOTE 189 study are PFS and overall survival. Further patient-relevant outcomes are outcomes on morbidity, health-related quality of life and AEs.

The study started in 2016 and is still ongoing. The company used the data cut-off of the first prespecified interim analysis from 8 November 2017 for the adjusted indirect comparison. In addition, the company presented the results of the final analysis from 20 May 2019.

Study KEYNOTE 407

As already described in the dossier assessment on project A19-31, KEYNOTE 407 is an ongoing RCT on the comparison of pembrolizumab + carboplatin-based chemotherapy with a carboplatin-based chemotherapy. The study included adults with histologically or cytologically confirmed diagnosis of squamous NSCLC in the metastatic stage (stage IV). Patients had to have received no prior systemic treatment for this stage. For patients who had received adjuvant or neoadjuvant therapy, this treatment had to be completed at least 12 months prior to the development of metastases. Included patients had to have an ECOG PS of 0 or 1. Patients with active brain metastases were excluded from the study.

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 Assay.

The study included a total of 559 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab + carboplatin-based chemotherapy (N = 278) or to treatment with only carboplatin-based chemotherapy (N = 281). Randomization was stratified by type of taxane-based chemotherapy (paclitaxel/nab-paclitaxel), PD-L1 expression (< 1%/≥ 1%) and geographical region (East Asia/not East Asia).

Pembrolizumab, carboplatin and nab-paclitaxel were administered in compliance with the SPCs [41,43,64] or the AM-RL on off-label use (Appendix VI to Section K [1]). Neither the SPCs [41,42] nor the AM-RL on off-label use (Appendix VI to Section K [1]) contain information on the dosage of paclitaxel in combination with carboplatin. In the study, paclitaxel was administered as 3-hour infusion at a dosage of 200 mg/m^2 BSA. Treatment in the intervention arm was generally restricted by the maximum number of allowed cycles (35 cycles) of pembrolizumab. Patients were treated until disease progression, complete response, unacceptable side effects, or study discontinuation upon the physician's or patient's discretion.

After discontinuation of the study medication (e.g. due to disease progression), the patients in both treatment arms could receive subsequent therapies. There was no limitation regarding the type of subsequent therapy. Moreover, suitable patients with disease progression were allowed to switch from treatment with the comparator therapy to monotherapy with pembrolizumab.

The primary outcomes of the study are PFS and overall survival. Patient-relevant secondary outcomes are morbidity, health-related quality of life, and AEs.

The study started in 2016 and is still ongoing. The company used the data cut-off of the second prespecified interim analysis from 3 April 2018 for the adjusted indirect comparison. In addition, the company presented the results of the final analysis from 9 May 2019.

Subpopulations of the studies KEYNOTE 189 and KEYNOTE 407 presented by the company

From the studies on the comparator side of the indirect comparison, there is also only a subpopulation relevant in each case. In contrast to cemiplimab + platinum-based chemotherapy, the administration of pembrolizumab + platinum-based chemotherapy is approved in NSCLC regardless of PD-L1 expression [43]. The KEYNOTE 189 study included patients with a PD-L1 expression of the tumour cells of < 50%, whereas the KEYNOTE 407 study included patients irrespective of the PD-L1 expression of the tumour cells. Patients with PD-L1 expression of tumour cells from 1 to 49% are relevant for the benefit assessment.

However, the company used the subpopulations of both KEYNOTE studies, which had already been used in the previous benefit assessment procedures 2019-04-01-D-447 + 2019-04-01-D-448. Both subpopulations were limited to patients with PD-L1 expression of tumour cells of < 50% for whom, according to a retrospective investigator survey carried out by the company for the procedures of the time, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K [1]). These subpopulations were referred to as "TPC populations" (see also KEYNOTE 024 in Section I 3.1.2). This procedure means that 126 of 260 (48%) patients in the intervention and comparator arm with non-squamous NSCLC histology (KEYNOTE 189) who were assigned to therapy with carboplatin are not included in the analysis. In the case of squamous histology (KEYNOTE 407), this limitation affects 91 out of 401 (23%) patients. For the benefit assessment, the company used the TPC populations, which also include patients with a PD-L1 expression of the tumour cells of < 1%, however. This approach is not appropriate and is explained below (see Section I 4.1.3).

Patient characteristics presented cannot be meaningfully interpreted

In Module 4 E, the company presented the patient characteristics for the EMPOWER-Lung 3 study for the subpopulation of patients with a PD-L1 expression of the tumour cells from 1 to 49% separately according to squamous (N = 75) and non-squamous (N = 72) histology. For the KEYNOTE 189 and KEYNOTE 407 studies, the company's Module 4 E presented patient characteristics of a subpopulation with PD-L1 expression of tumour cells of ≥ 50% (including < 1%) which was restricted post hoc according to the investigator's assessment for carboplatin treatment. The different operationalizations for the formation of the subpopulations in the EMPOWER-Lung 3 study compared with the KEYNOTE studies mean that the subpopulations presented by the company do not have the similarity required for an indirect comparison. Therefore, a meaningful interpretation of the patient characteristics presented is not possible.

Information on treatment duration and observation period, as well as on subsequent therapies is incomplete or missing

Information on treatment duration is only available for the EMPOWER-Lung 3 study. Information on the observation period and subsequent therapies is completely missing for all studies.

Therefore, it is not possible to assess the similarity of the studies with regard to the patients' treatment durations, observation periods, and subsequent therapies.

I 4.1.3 Similarity of the studies for the indirect comparison

In the following, key aspects are discussed that affect the similarity of the studies for conducting an adjusted indirect comparison and that go beyond the study characteristics described in Section I 4.1.2.

Similarity of the study populations

In principle, the 3 studies EMPOWER-Lung 3, KEYNOTE 189 and KEYNOTE 407 have a similar study design. However, it can be assumed that the presented subpopulations do not have the similarity required for an indirect comparison. This is due to the fact that the study populations of the KEYNOTE studies include a relevant number of patients who are not included in the research question. Based on the approval of cemiplimab + platinum-based chemotherapy, patients with a PD-L1 expression of the tumour cells of 1 to 49% are relevant for the present research question. However, the proportion of patients with a PD-L1 expression of the tumour cells of < 1%, who are therefore not part of the research question, is 49% in the intervention versus 52% in the comparator arm in the KEYNOTE 189 study, and 45% versus 50% in the KEYNOTE 407 study. The approach of the company to include patients with a PD-L1 expression of tumour cells of < 1% in the similarity test is not appropriate.

Moreover, analogous to research question 1, it must be assumed that there is a relevant difference in the study populations between the KEYNOTE 189 and KEYNOTE 407 studies and the EMPOWER-Lung 3 study due to the post-hoc restriction of the subpopulation to those patients for whom, according to a retrospective survey, carboplatin was a suitable treatment option in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K [1]).

Usability of the indirect comparisons presented by the company

The similarity check is a central prerequisite for the inclusion of studies in an adjusted indirect comparison [2,65,66]. According to the similarity assumption, all studies considered are comparable with regard to possible effect modifiers across all interventions. In addition to potential effect modifiers (e.g. patient characteristics, study characteristics, intervention characteristics), methodological factors (e.g. outcome characteristics) must also be taken into account [67].

The patient characteristics presented by the company in Module 4 E cannot be meaningfully interpreted, as the subpopulations formed do not have the similarity required for an indirect comparison. The information on treatment duration and observation period, on subsequent therapies and on the distribution of the platinum component for the presented subpopulations of the EMPOWER-Lung 3 study and the KEYNOTE 189 and KEYNOTE 407 studies is incomplete or missing entirely.

In summary, in particular the post-hoc restriction of the subpopulation described above and the high proportion of patients on the comparator side of the indirect comparison, which is not covered by research question 2, mean that the subpopulations presented do not have the similarity required for an indirect comparison, and therefore the 2 indirect comparisons of

cemiplimab + platinum-based chemotherapy in comparison with the ACT presented by the company are not usable.

Furthermore, although the company presented results for the outcome categories of mortality, morbidity, health-related quality of life and side effects for the total population of the EMPOWER-Lung 3 study, it only provided information on the outcome of overall survival for the subpopulations of patients with a PD-L1 expression of the tumour cells from 1 to 49% and non-squamous or squamous histology it had formed, and only used this outcome for the indirect comparisons. The company justified the latter by stating that no data were available for further outcomes for the subpopulation of interest (PD-L1 expression of tumour cells from 1 to 49%) of the KEYNOTE 189 and KEYNOTE 407 studies. For this reason alone, no sufficient data is available for balancing benefit and harm.

I 4.2 Results on added benefit

The data presented by the company for the assessment of the added benefit of cemiplimab + platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or with metastatic NSCLC expressing PD-L1 in 1 to ≥ 49% of tumour cells, with no EGFR, ALK or ROS1 aberrations, are not suitable for deriving an added benefit of cemiplimab + platinum-based chemotherapy compared with the ACT. This results in no hint of added benefit of cemiplimab + platinum-based chemotherapy in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

The data presented by the company for the assessment of the added benefit of cemiplimab + platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or with metastatic NSCLC expressing PD-L1 in 1 to ≥ 49% of tumour cells, with no EGFR, ALK or ROS1 aberrations, are not suitable for deriving an added benefit of cemiplimab + platinum-based chemotherapy compared with the ACT. An added benefit for these patients is therefore not proven.

The assessment described above deviates from that of the company, which derived a non-quantifiable added benefit in comparison with pembrolizumab + platinum-based chemotherapy as ACT for all patients in the newly approved therapeutic indication of cemiplimab + platinum-based chemotherapy – regardless of PD-L1 expression and NSCLC histology.

I 5 Probability and extent of added benefit – summary

Table 11 summarizes the result of the assessment of the added benefit of cemiplimab + platinum-based chemotherapy in comparison with the ACT.

Table 11: Cemiplimab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab as monotherapy**[c] or ▪ atezolizumab as monotherapy or ▪ cemiplimab as monotherapy or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC)	Added benefit not proven[d]

Table 11: Cemiplimab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
2	First-line treatment of adult patients[b] with NSCLC expressing PD-L1 in **≥ 1% and < 50%** of tumour cells, with no EGFR, ALK or ROS1 aberrations Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definitive chemoradiation, or ▪ patients with metastatic NSCLC	▪ **Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy**[c] (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ **pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel**[c] (only for patients with ECOG PS 0–1 and squamous NSCLC) or ▪ atezolizumab as monotherapy (only for patients with PD-L1 expression ≥ 10% in tumour-infiltrating immune cells) or ▪ atezolizumab in combination with bevacizumab, paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ atezolizumab in combination with nab-paclitaxel and carboplatin (only for patients with ECOG PS 0–1 and non-squamous NSCLC) or ▪ nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy (only for patients with ECOG PS 0–1) or ▪ carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed); see also Appendix VI to Section K of the Pharmaceutical Directive[e] (only for patients with ECOG PS 2) or ▪ carboplatin in combination with nab-paclitaxel (only for patients with ECOG PS 2)	Added benefit not proven[d]

Table 11: Cemiplimab + platinum-based chemotherapy – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients are not indicated for definitive chemoradiation or for definitive local therapy, and that no molecularly stratified therapy (against BRAF, KRAS G12C, METex14 or RET) is an option for the patients at the time of treatment with cemiplimab in combination with platinum-based chemotherapy.
c. In the present therapeutic indication, pembrolizumab is approved as monotherapy and in combination with platinum-containing chemotherapy only for patients with metastatic NSCLC.
d. Only patients with an ECOG PS of 0 or 1 were included in the studies for the indirect comparison.
e. Regarding carboplatin in combination with a third-generation cytostatic agent: In each case, the choice of the platinum component (carboplatin or cisplatin) was to be based on the different toxicity profiles of the 2 substances and on existing comorbidities; see Appendix VI to Section K of the Pharmaceutical Directive [1].

ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: exon 14 of the MET gene; nab: albumin-bound nanoparticles; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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