IQWiG Reports – Commission No. A21-98

Cemiplimab (non-small cell lung cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Cemiplimab (nicht kleinzelliges Lungenkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ALK	anaplastic lymphoma kinase
AM-RL	Pharmaceutical Directive
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
ROS1	C-ros oncogene 1
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
TPS	Tumour Proportion Score

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug cemiplimab. 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 21 July 2021.

Research question

The aim of the present report was to assess the added benefit of cemiplimab in comparison with pembrolizumab as appropriate comparator therapy (ACT) for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) whose tumours express programmed cell death ligand 1 (PD-L1) in ≥ 50% of the tumour cells and have no aberrations due to epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or C-ros oncogene 1 (ROS1). Treatment is intended for:

- patients with locally advanced NSCLC who are not candidates for definite radiochemotherapy, or
- patients with metastatic NSCLC.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of cemiplimab

Therapeutic indication[a]	**ACT**[b]
First-line treatment of adult patients with NSCLC whose tumours express PD-L1 in ≥ 50% of the tumour cells and have no aberrations due to EGFR, ALK or ROS1. Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definite radiochemotherapy, or ▪ patients with metastatic NSCLC	Pembrolizumab[c] as monotherapy
a. For the patients covered by the present field of application, it is assumed that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. b. Presentation of the respective ACT specified by the G-BA. c. In the present therapeutic indication, pembrolizumab is approved as monotherapy only for patients with metastatic NSCLC. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1	

The company followed the specification of the ACT.

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

Study pool and study design

Concurring with the company, no relevant study on the direct comparison of cemiplimab versus pembrolizumab in the present therapeutic indication was identified from the check of the completeness of the study pool. Therefore, the company presented adjusted indirect comparisons according to Bucher for the assessment of cemiplimab in comparison with pembrolizumab using the common comparator platinum-based chemotherapy.

For cemiplimab, the company's study pool comprised the randomized controlled trial (RCT) R2810-ONC-1624 and for pembrolizumab, it included the RCTs KEYNOTE 024 and KEYNOTE 042 as well as KEYNOTE 042-China. As no information on the patient characteristics of the relevant subpopulation (with PD-L1 Tumour Proportion Score [TPS] ≥ 50%) is available for the KEYNOTE 042-China study, this study is not considered below.

Analyses presented by the company cannot be used for the indirect comparison and the similarity of the studies cannot be assessed with sufficient certainty

The company submitted 3 independently calculated, adjusted indirect comparisons to derive the added benefit. First, an indirect comparison of the R2810-ONC-1624 study for cemiplimab, and of the KEYNOTE 024 study for pembrolizumab. For the KEYNOTE 042 study with pembrolizumab, the company presented 2 indirect comparisons of the studies R2810-ONC-1624 and KEYNOTE 042, separated by squamous and non- squamous histology. For the assessment of the similarity of the studies, various aspects cannot be assessed with sufficient certainty due to missing information (especially on the therapies in the comparator arm of study R2810-ONC-1624). In addition, due to the restriction of the subpopulation of the KEYNOTE 042 study to those patients for whom carboplatin was a suitable treatment option according to the Pharmaceutical Directive (AM-RL) on the off-label use (Appendix VI to Section K), it can be assumed that the KEYNOTE 042 study differs relevantly from the studies R2810-ONC-1624 and KEYNOTE 024 with regard to the study population in the common comparator. The analyses presented by the company can therefore not be used for the benefit assessment. Moreover, the approach of the company to present 3 independently calculated, adjusted indirect comparisons is not appropriate.

Study with cemiplimab: R2810-ONC-1624

R2810-ONC-1624 is an ongoing, open-label RCT on the comparison of cemiplimab with a platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed stage IIIB, IIIC or IV NSCLC without EGFR mutation and without ALK translocation and ROS1 translocation, whose tumours had a PD-L1 expression ≥ 50%. Patients were not allowed to have received any prior systemic therapy for advanced or metastatic disease. In addition, definitive radiochemotherapy had to be unsuitable for the patients.

The study R2810-ONC-1624 included a total of 710 patients, assigned in a 1:1 ratio either to treatment with cemiplimab (N = 356) or with a platinum-based combination chemotherapy (N = 354). The treatment options were as follows: pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin, paclitaxel + carboplatin, gemcitabine + cisplatin or gemcitabine + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous histology. The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the R2810-ONC-1624 study. After at least 4 cycles, patients with non-squamous histology could receive maintenance treatment with pemetrexed.

Prior to August 2018, PD-L1 expression testing was not performed according to the 22C3 assay instructions. The company presented the results of a subpopulation that comprised the patients enrolled before August 2018, in whom PD-L1 expression of the tumours of ≥ 50% was verified in a retest, as well as the patients included as of August 2018. The subpopulation formed by the company is relevant for the benefit assessment and comprises N = 283 patients in the intervention arm and N = 280 patients in the chemotherapy arm. However, the company presented results for this subpopulation only for the outcomes in the categories "mortality", "morbidity" and "health-related quality of life". For side effects, the company used the results of the safety population (n = 697).

Treatment was given until disease progression, occurrence of unacceptable toxicity, death or withdrawal of consent.

After disease progression and confirmed suitability, patients in the cemiplimab arm could be treated with cemiplimab in combination with platinum-based combination chemotherapy for a further 108 weeks (4 cycles). Patients in the comparator arm could switch to treatment with cemiplimab as monotherapy (up to 108 weeks). However, cemiplimab is not approved for treatment after prior chemotherapy.

Primary outcomes of the study were "overall survival" and "progression-free survival (PFS)". Patient-relevant secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events (AEs).

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

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

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based combination 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 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 until disease progression, occurrence of unacceptable side effects, or discontinuation of the study due to decision by the investigator or the patient.

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

KEYNOTE 042

As already described in the dossier assessments on the projects A19-30 and A19-31, KEYNOTE 042 is an ongoing, open-label RCT. The study compared pembrolizumab with a combination of carboplatin and either paclitaxel or pemetrexed. A total of 1274 patients were randomly allocated to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637) in a 1:1 ratio. The study included adults with histologically or cytologically confirmed diagnosis of NSCLC with locally advanced or metastatic tumours with PD-L1 expression ≥ 1%. Prior systemic treatment was not allowed in the study.

Patients with PD-L1 expression ≥ 50% (N = 599) are relevant for the benefit assessment. Data for the entire relevant subpopulation are only available from the publication Mok 2019 for the outcome "overall survival". The benefit assessment procedures 2019-04-01-D-447 + 2019-04-01-D-448 provide further analyses, which are, however, limited to those patients for whom carboplatin represented a suitable treatment option according to a retrospective investigator survey carried out by the company for the procedures of the time in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K). These analyses are only available separately for patients with squamous (N = 176) and non- squamous histology (N = 120) and comprise just under 50% of the relevant subpopulation.

The treatment options in the comparator arm of the study were as follows: pemetrexed + carboplatin or paclitaxel + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous histology. Patients with non-squamous histology received carboplatin for a maximum of 4 to 6 cycles in the KEYNOTE 042 study. After at least 4 cycles, patients with non-squamous histology could receive maintenance treatment with pemetrexed, which was also recommended.

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

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

Similarity of the common comparator platinum-based combination chemotherapy in the studies

For the present indirect comparison, the company chose "platinum-based combination chemotherapy" as common comparator. In the 3 included studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042, this includes different platinum-based combination chemotherapies. These differed between the studies: For example, paclitaxel was only a treatment option in combination with cisplatin on the cemiplimab side of the indirect comparison, and in the KEYNOTE 042 study, only carboplatin was administered as the platinum component.

Platinum component of the common comparator

In R2810-ONC-1624, the platinum-based combination chemotherapy was chosen prior to randomization at the discretion of the investigator and had to comply with the local treatment standard. There is no information on possible selection criteria of the platinum components in the studies KEYNOTE 024 and KEYNOTE 042; in each case, there is only the information that the choice took place on an individual basis prior to randomization.

For study R2810-ONC-1624, no information is available on the distribution of the platinum component in the relevant subpopulation. In the safety population of the R2810-ONC-1624 study, approximately one quarter of the patients in the comparator arm received cisplatin, and the remaining patients received carboplatin. About 1 third of the patients in the comparator arm of the KEYNOTE 024 study received cisplatin, and the remaining patients received carboplatin. In the KEYNOTE 042 study, only carboplatin was administered.

As described above, the present analyses from the KEYNOTE 042 study (except for the outcome "overall survival") only include just under 50% of the relevant subpopulation, as this was restricted post hoc 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 the off-label use (Appendix VI to Section K). The company did not make such a restriction of the population for the studies R2810-ONC-1624 and KEYNOTE 024.

Chemotherapy component of the common comparator

In the R2810-ONC-1624 study, patients could receive pemetrexed (only in case of non-squamous histology), gemcitabine as well as paclitaxel, each in combination with cisplatin or carboplatin. Deviating from this, paclitaxel in combination with cisplatin was no treatment option in the KEYNOTE 024 study nor in the KEYNOTE 042 study. Moreover, patients in KEYNOTE 042 could not be treated with gemcitabine.

More than 80% of the patients with non-squamous NSCLC received pemetrexed in the KEYNOTE 024 study. There is no information for the relevant subpopulation of the studies R2810-ONC-1624 and KEYNOTE 042. 70% of the 196 patients with non-squamous NSCLC of the safety population of R2810-ONC-1624 received pemetrexed.

In the KEYNOTE 024 study, 81% of the patients with squamous histology received gemcitabine in addition to the platinum component; the remaining patients received paclitaxel. In the KEYNOTE 042 study, only paclitaxel could be administered in addition to carboplatin. There is no information for the relevant subpopulation of the R2810-ONC-1624 study.

In the comparator arm of the KEYNOTE 024 study, a total of 11% of the patients (with squamous and non-squamous histology), and at least 38% of the patients in KEYNOTE 042 received paclitaxel; concrete information is not available. There is no information for the relevant subpopulation of the R2810-ONC-1624 study either. In the safety population of the R2810-ONC-1624 study, about 40% of the patients (with squamous and non-squamous histology) in the comparator arm were treated with paclitaxel.

Maintenance treatment in the common comparator

In the KEYNOTE 024 study, 37% of the patients with non-squamous histology received maintenance therapy with pemetrexed, although this maintenance therapy was recommended according to the study documents. In the studies R2810-ONC-1624 and KEYNOTE 042, administration of a maintenance treatment was at the investigator's discretion and was recommended in the KEYNOTE 042 study. There is no information for the relevant subpopulation of the two studies.

Summary

Data on the proportions of each platinum-based combination chemotherapy received in the comparator arm of the relevant subpopulation are missing, in particular, for the R2810-ONC-1624 study. Therefore, the similarity of the common comparators cannot be assessed with sufficient certainty.

Moreover, it must be assumed that the KEYNOTE 042 study differs relevantly from the studies R2810-ONC-1624 and KEYNOTE 024 with regard to the study population in the common comparator due to the post hoc restriction of the subpopulation to those patients for whom, according to a retrospective survey, carboplatin presents a suitable treatment option in accordance with the AM-RL for the off-label use (Appendix VI to Section K).

Similarity of the studies and usability of the analyses presented by the company in the adjusted indirect comparison

Similarity is a key requirement for the consideration of studies in the adjusted indirect comparison. Basically, the 3 studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 have a very similar study design and the patient populations are also sufficiently similar. However, certain aspects cannot be assessed with sufficient certainty due to missing

information (especially on the therapies in the comparator arm of study R2810-ONC-1624). Moreover, it must be assumed that the KEYNOTE 042 study differs relevantly from the studies R2810-ONC-1624 and KEYNOTE 024 with regard to the study population in the common comparator due to the post hoc restriction of the subpopulation to those patients for whom, according to a retrospective survey, carboplatin presents a suitable treatment option in accordance with the AM-RL for the off-label use (Appendix VI to Section K). Moreover, the results of the 3 studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 were not adequately prepared and can therefore not be used.

Further notes on the data presented by the company

At the time point of the relevant data cut-off, 107 (approx. 38%) of the patients in the comparator arm of the study R2810-ONC-1624 were receiving cemiplimab as subsequent therapy. This is no approved treatment option after prior chemotherapy. Moreover, it is unclear which data are considered in the analysis of the outcome "overall survival". Regardless of this, there is no statistically significant difference between the treatment arms for the outcome "overall survival" in any of the indirect comparisons presented by the company.

For the study R2810-ONC-1624, the company only presented analyses on AEs) for the safety population and not for the relevant subpopulation. In addition, the data on frequent AEs provided by the company for the safety population do not meet the requirements of the dossier templates.

Results

The data presented by the company for the assessment of the added benefit of cemiplimab in the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive radiochemotherapy, or adult patients with metastatic NSCLC whose tumours express PD-L1 in ≥ 50% of the tumour cells and who have no EGFR, ALK or ROS1 aberrations, are not suitable for deriving an added benefit of cemiplimab compared with the ACT. This resulted in no hint of an added benefit of cemiplimab in comparison with the ACT; an added benefit is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug cemiplimab 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 [1,2].

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

Table 3 shows a summary of probability and extent of the added benefit of cemiplimab.

Table 3: Cemiplimab – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
First-line treatment of adult patients with NSCLC whose tumours express PD-L1 in ≥ 50% of the tumour cells and have no aberrations due to EGFR, ALK or ROS1. Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definite radiochemotherapy, or ▪ patients with metastatic NSCLC	Pembrolizumab[c] as monotherapy	Added benefit not proven
a. For the patients covered by the present field of application, it is assumed that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. b. Presentation of the respective ACT specified by the G-BA. c. In the present therapeutic indication, pembrolizumab is approved as monotherapy only for patients with metastatic NSCLC. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of cemiplimab in comparison with pembrolizumab as ACT for the first-line treatment of adult patients with NSCLC whose tumours express PD-L1 in ≥ 50% of the tumour cells and have no aberrations due to EGFR, ALK or ROS1. Treatment is intended for:

- patients with locally advanced NSCLC who are not candidates for definite radiochemotherapy, or
- patients with metastatic NSCLC.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of cemiplimab

Therapeutic indication[a]	**ACT**[b]
First-line treatment of adult patients with NSCLC whose tumours express PD-L1 in ≥ 50% of the tumour cells and have no aberrations due to EGFR, ALK or ROS1. Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definite radiochemotherapy, or ▪ patients with metastatic NSCLC	Pembrolizumab[c] as monotherapy
a. For the patients covered by the present field of application, it is assumed that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. b. Presentation of the respective ACT specified by the G-BA. c. In the present therapeutic indication, pembrolizumab is approved as monotherapy only for patients with metastatic NSCLC. ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1	

The company followed the specification of the ACT.

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on cemiplimab (status: 3 June 2021)
- bibliographical literature search on cemiplimab (last search on 28 May 2021)
- search in trial registries/trial results databases for studies on cemiplimab (last search on 3 June 2021)
- search on the G-BA website for cemiplimab (last search on 3 June 2021)
- bibliographical literature search on the ACT (last search on 28 May 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 3 June 2021)
- search on the G-BA website for the ACT (last search on 3 June 2021)

To check the completeness of the study pool:

- search in trial registries for studies on cemiplimab (last search on 3 August 2021); for search strategies, see Appendix A of the full dossier assessment

- search in trial registries for studies on the ACT (last search on 12 August 2021); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, no relevant study on the direct comparison of cemiplimab versus pembrolizumab in the present therapeutic indication was identified from the check of the completeness of the study pool.

Therefore, the company presented adjusted indirect comparisons according to Bucher [3] for the assessment of cemiplimab in comparison with pembrolizumab using the common comparator platinum-based chemotherapy.

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

2.3.1 Studies included

The company therefore presented adjusted indirect comparisons using the common comparator platinum-based chemotherapy for the assessment of the added benefit of cemiplimab. The company justifies the choice of the common comparator by stating that the identified study with the drug to be assessed (cemiplimab) is the only RCT in the relevant therapeutic indication and thus a comparison with the ACT specified by the G-BA (pembrolizumab) is only possible with a platinum-based combination chemotherapy as common comparator.

Concurring with the company, a platinum-based combination chemotherapy was used as common comparator for an adjusted indirect comparison in the benefit assessment.

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

Table 5: Study pool – RCT, indirect comparison: cemiplimab 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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
Cemiplimab vs. platinum-based combination chemotherapy						
R2810-ONC-1624	Yes	Yes	No	Yes [4]	Yes [5,6]	Yes [7]
Pembrolizumab vs. platinum-based combination chemotherapy						
KEYNOTE 024	No	No	Yes	No	Yes [8,9]	Yes [10-22]
KEYNOTE 042	No	No	Yes	No	Yes [23,24]	Yes [20-22,25-31]
KEYNOTE 042 - China	No	No	Yes	No	Yes [32]	Yes [33]

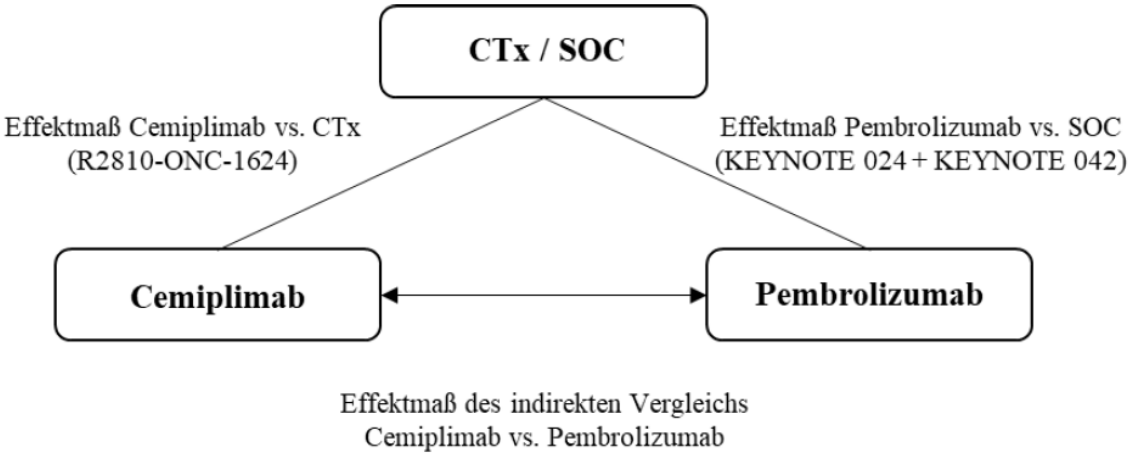
a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool concurs with that of the company.

For cemiplimab, the company's study pool comprised the RCT R2810-ONC-1624 and for pembrolizumab, it included the RCTs KEYNOTE 024 and KEYNOTE 042 as well as KEYNOTE 042-China. 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 TPS ≥ 50%) is available for the KEYNOTE 042-China study, the company did not consider this study further 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 indirect comparison.



Effektmaß: effect measure
SOC: System Organ Class
CTx: Chemotherapy
Effektmaß des indirekten Vergleichs: effect measure of the indirect comparison

Figure 1: Study pool for the indirect comparison between cemiplimab and the ACT pembrolizumab

Analyses presented by the company cannot be used for the indirect comparison and the similarity of the studies cannot be assessed with sufficient certainty.

The company submitted 3 independently calculated, adjusted indirect comparisons to derive the added benefit. First, an indirect comparison of the R2810-ONC-1624 study for cemiplimab, and of the KEYNOTE 024 study for pembrolizumab. For the KEYNOTE 042 study with pembrolizumab, the company used the results of previous benefit assessment procedures. However, these are only available separately for patients with squamous and non-squamous histology. Therefore, the company presented 2 further indirect comparison of the studies R2810-ONC-1624 and KEYNOTE 042, each separated by squamous and non-squamous histology. To derive the added benefit, the company considered each of these indirect comparisons in isolation. The company based its claim for added benefit on advantages of cemiplimab for the outcomes “PFS” and “serious adverse events (SAEs)” in only one of the indirect comparisons conducted (studies R2810-ONC-1624 and KEYNOTE 042 in patients with non-squamous histology).

For the assessment of the similarity of the studies, various aspects cannot be assessed with sufficient certainty due to missing information (especially on the therapies in the comparator arm of study R2810-ONC-1624) (see Section 2.3.2). In addition, due to the restriction of the subpopulation of the KEYNOTE 042 study to those patients for whom carboplatin was a suitable treatment option according to the AM-RL on the off-label use (Appendix VI to Section K, [34]), it can be assumed that the KEYNOTE 042 study differs relevantly from the studies R2810-ONC-1624 and KEYNOTE 024 with regard to the study population in the common

comparator. The analyses presented by the company can therefore not be used for the benefit assessment.

Moreover, the approach of the company to present 3 independently calculated, adjusted indirect comparisons is not appropriate. What would be required before calculating an indirect comparison is the meta-analytical summary of the results on the pembrolizumab side of the indirect comparison.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: cemiplimab 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 vs. platinum-based combination chemotherapy						
R2810-ONC-1624	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed stage IIIB, IIIC or IV NSCLC[b], PD-L1 expression ≥ 50%, without EGFR mutation, without ALK and ROS1-translocations, ECOG PS ≤ 1 and ▪ without prior systemic therapy[c] or ▪ not suitable for definitive radiochemotherapy[d]	Cemiplimab (N = 356) platinum-based combination chemotherapy[e] (N = 354) relevant subpopulation thereof[f]: cemiplimab (n = 283) platinum-based combination chemotherapy[e] (N = 280)	Screening: up to 28 days treatment: until progression[g], unacceptable toxicity, death or withdrawal of consent or a maximum of 108 weeks cemiplimab observation: outcome-specific[h], at most until death	138 centres in Australia, Belarus, Brazil, Bulgaria, Chile, China, Columbia, Czech Republic, Georgia, Greece, Hungary, Jordan, Lebanon, Malaysia, Mexico, Philippines, Poland, Romania, Russia, Spain, Taiwan, Thailand, Turkey, Ukraine 05/2017–ongoing data cut-offs: 27 September 2019 (first interim analysis) 1 March 2020[i]	Primary: overall survival, PFS secondary: morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: cemiplimab 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 combination chemotherapy						
KEYNOTE 024	RCT, open-label, parallel	Adult patients with histologically or cytologically confirmed stage IV NSCLC, PD-L1 expressing tumours (TPS ≥ 50%) without EGFR mutation or ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[c]	Pembrolizumab (N = 154) platinum-based combination chemotherapy[e] (N = 151)	Screening: 30 days prior to the start of treatment treatment: until progression (or beyond, as long as the patient benefits), unacceptable toxicity, study discontinuation due to decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[j] observation: outcome-specific[h], at most until death	142 centres in Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Spain, United Kingdom, USA 09/2014–05/2016[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 aecondary: overall survival, morbidity, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: cemiplimab 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	Adult patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC, PD-L1 expressing tumours (TPS ≥ 1%) without EGFR mutation or ALK translocation, ECOG PS ≤ 1, without previous systemic therapy[c]	Pembrolizumab (N = 637) platinum-based combination chemotherapy[e] (N = 637) relevant subpopulation thereof[f]: pembrolizumab (n = 299) platinum-based combination chemotherapy[e] (N = 300)	Screening: 30 days prior to the start of treatment treatment: until progression, unacceptable toxicity, study discontinuation due to decision by the investigator or the patient, complete response or a maximum of 35 cycles of pembrolizumab[j] outcome-specific[h], at most until death	196 centres in Argentina, Brazil, Bulgaria, Canada, Chile, China, Columbia, 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–ongoing data cut-offs: 26 February 2018 4 September 2018 (final PFS analysis)	Primary: overall survival secondary: AEs

Table 6: Characteristics of the study included – RCT, direct comparison: cemiplimab 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 consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Squamous or non-squamous.
c. Without prior systemic therapy for the metastatic NSCLC stage (KEYNOTE 024) or the advanced or metastatic NSCLC stage (R2810-ONC-1624, KEYNOTE 042).
d. In NSCLC stage IIIB and IIIC.
e. Within the framework of the chemotherapy, the following platinum-based combination chemotherapies were chosen on an individual basis prior to randomization: pemetrexed + cisplatin (R2810-ONC-1624, KEYNOTE 024), pemetrexed + carboplatin (R2810-ONC-1624, KEYNOTE 024, KEYNOTE 042), paclitaxel + cisplatin (R2810-ONC-1624), paclitaxel + carboplatin (R2810-ONC-1624, KEYNOTE 024, KEYNOTE 042), gemcitabine + cisplatin (R2810-ONC-1624, KEYNOTE 024) or gemcitabine + carboplatin (R2810-ONC-1624, KEYNOTE 024). Combinations with pemetrexed were only allowed for patients with non-squamous histology.
f. Only those patients in whom the PD-L1 expression ≥ 50% determined by a 22C3 assay using immunohistochemistry was verified in a retest.
g. After progression and confirmed eligibility, patients in the cemiplimab arm could be treated with cemiplimab in combination with platinum-based combination chemotherapy (4 cycles) for a further 108 weeks, and patients in the comparator arm could switch to treatment with cemiplimab monotherapy (up to 108 weeks). After the primary outcome “overall survival” had been reached at the time of the 9th protocol amendment, patients in the comparator arm were allowed to switch to cemiplimab even before disease progression.
h. Outcome-specific information is provided in Table 9.
i. Since cemiplimab was superior to platinum-based combination chemotherapy with respect to overall survival, the final analysis was conducted at the time point of the data cut-off of the second interim analysis (1 March 2020). This second data cut-off was prospectively planned to be performed after 238 events for the outcome "overall survival” had been reached. All patients in the treatment arm with solely platinum-based combination chemotherapy were offered to switch to treatment with cemiplimab.
j. Patients in the pembrolizumab arm (KEYNOTE 024 and KEYNOTE 042) could temporarily discontinue treatment after confirmed response or after achievement of the maximum number of treatment cycles for pembrolizumab, and restart treatment with pembrolizumab at the investigator’s discretion (“second course phase“) after subsequent confirmed progression (if certain conditions regarding previous treatment duration and disease status were met). It is to be assumed that only < 5% of the patients in the total study population (KEYNOTE 024 and KEYNOTE 042) reached the “second course phase“.

Table 6: Characteristics of the study included – RCT, direct comparison: cemiplimab 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]
k. Since pembrolizumab was superior to platinum-based combination chemotherapy with respect to overall survival, the final analysis was conducted at the time point of the data cut-off of the second interim analysis (9 May 2016). This second data cut-off was prospectively planned to be performed after 175 events for the outcome "PFS" had been reached. All patients in the treatment arm with solely platinum-based combination chemotherapy were offered to switch to treatment with pembrolizumab. l. Patients with NSCLC with high PD-L1 expression, without EGFR mutation or ALK translocation (WT; TPS ≥ 50%); data on this subpopulation are available from previous benefit assessment procedures (2019-04-01-D-447 + 2019-04-01-D-448 [35,36]), but limited to patients treated with carboplatin according to the criteria of the Pharmaceutical Directive (AM-RL) for off-label use (Appendix VI to Section K [2]) and only separately for patients with squamous (N = 176) and non-squamous histology (N = 120). AE: adverse event; ALK: anaplastic lymphoma kinase; AM-RL: Pharmaceutical Directive; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; n: relevant subpopulation; n: relevant subpopulation; N: number of randomized patients; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; RCT: randomized controlled trial; ROS1: c-ros oncogene 1; TPS: Tumour Proportion Score; WT: wild type					

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

Study	Intervention	Comparison
Cemiplimab vs. platinum-based combination chemotherapy		
R2810-ONC-1624	Cemiplimab 350 mg IV (as 30-minute infusion) on day 1 of a 21-day cycle	Platinum-based combination chemotherapy[a] for 4 to 6 cycles: <u>induction phase (4 to 6 cycles)</u> <u>only non-squamous:</u> Pemetrexed 500 mg/m^2, BSA, IV, + cisplatin 75 mg/m^2 BSA, IV or carboplatin AUC 5 or 6 mg/mL/min, IV on day 1 of each 21-day cycle <u>non-squamous and squamous:</u> paclitaxel 200 mg/m^2 BSA, IV + cisplatin 75 mg/m^2 BSA, IV or carboplatin AUC 5 or 6 mg/mL/min, IV on day 1 of each 21-day cycle or gemcitabine 1 250 mg/m^2 BSA, IV on day 1 and 8 of each 21-day cycle + cisplatin 100 mg/m^2 BSA, IV or carboplatin AUC 5 or 6 mg/mL/min, IV on day 1 of each 21-day cycle <u>maintenance phase</u> <u>only non-squamous:</u> after at least 4 cycles of pemetrexed + cisplatin or pemetrexed + carboplatin, further treatment with pemetrexed 500 mg/m^2 BSA, IV, on day 1 of a 21-day cycle, was at the investigator's discretion
	Dose adjustments: ▪ cemiplimab: no dose adjustment allowed; treatment interruptions ≤ 84 days due to toxicity allowed[b] ▪ platinum-based combination chemotherapy: dose adjustments allowed according to regional guidelines or standard health care	

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

Study	Intervention Comparison
	Permitted pretreatment ▪ adjuvant or neoadjuvant platinum-based combination chemotherapy (following surgery and/or radiotherapy) ≥ 6 months before the development of recurrent or metastatic disease **non-permitted pretreatment** ▪ other investigational preparations ▪ anti-PD-1 or anti-PD-L1 drugs ▪ other immunomodulators (e.g. with CTLA-4) ≤ 3 months before the first dose of the study medication ▪ systemic corticosteroids (> 10 mg prednisone/day or equivalent)[c] ≤ 14 days before randomization and during the study ▪ live vaccines **premedication** ▪ for cemiplimab in case of infusion-related reactions (from cycle 2 onwards) ▪ for platinum-based combination chemotherapy with paclitaxel: corticosteroids, diphenhydramine + H2 receptor antagonists ▪ for platinum-based combination chemotherapy with pemetrexed: corticosteroids, folic acid and vitamin B12 **concomitant treatment** ▪ bisphosphonates, denosumab for the treatment of bone metastasis allowed ▪ palliative radiotherapy allowed

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

Study	Intervention	Comparison
Pembrolizumab vs. platinum-based combination chemotherapy		
KEYNOTE 024	Pembrolizumab 200 mg IV (as 30-minute infusion) on day 1 of a 21-day cycle	Platinum-based combination chemotherapy[a] for 4 to 6 cycles: induction phase (4 to 6 cycles) only non-squamous: pemetrexed 500 mg/m^2, BSA, IV + cisplatin 75 mg/m^2 BSA, IV or carboplatin: AUC of 5 or 6 mg/mL/min, IV on day 1 of each 21-day cycle non-squamous and squamous: gemcitabine 1250 mg/m^2 BSA, IV, on day 1 and 8 of a 21-week 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 or paclitaxel 200 mg/m^2 BSA, IV + carboplatin AUC of 5 or 6 mg/mL/min IV, day 1 of each 21-day cycle maintenance phase only non-squamous: after at least 4 cycles 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
	Dose adjustments: ▪ pembrolizumab: no dose adjustment allowed (according to the SPC), interruption allowed in case of side effects ▪ platinum-based combination chemotherapy: dose adjustments allowed according to the SPC	

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

Study	Intervention	Comparison
	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 ▪ radiotherapy[d] ▪ corticosteroids except for the treatment of AEs or used as premedication of a platinum-based combination chemotherapy used in the study ▪ bisphosphonate or anti-RANK-L inhibitors	
KEYNOTE 042	Pembrolizumab 200 mg, IV, on day 1 of a 21-day cycle	Carboplatin-based combination chemotherapy[a] for 4 to 6 cycles: induction phase (4 to 6 cycles) only non-squamous: pemetrexed 500 mg/m^2, BSA, IV + carboplatin AUC 5 or 6 mg/mL/min IV, day 1 of each 21-day cycle non-squamous and squamous: paclitaxel 200 mg/m^2 BSA, IV + carboplatin AUC 5 or 6 mg/mL/min IV, day 1 of each 21-day cycle maintenance phase only non-squamous: after at least 4 cycles of the carboplatin-based combination chemotherapy, further treatment with pemetrexed 500 mg/m^2 BSA, IV, on day 1 of a 21-day cycle, was at the investigator's discretion
	Dose adjustments: ▪ pembrolizumab: no dose adjustment allowed (treatment could be interrupted or discontinued) ▪ carboplatin-based combination chemotherapy: dose adjustments allowed according to the SPC	

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

Study	Intervention Comparison
	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 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** ▪ chemotherapies or immunotherapies other than pembrolizumab ▪ surgery for symptom or tumour control ▪ radiotherapy[d] ▪ live vaccines ▪ corticosteroids except for the treatment of AEs or used as premedication of a chemotherapy used in the study
a. Within the framework of the chemotherapy, the investigator chose an individual platinum-based combination therapy 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. Palliative radiotherapy for individual lesions was allowed, provided it was not a target lesion defined by RECIST version 1.1 and the therapy was not carried out for tumour control; study medication should be interrupted during radiotherapy. 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 protein1; PD-L1/PD-L2: programmed cell death ligand 1/2; RANKL: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours	

Study design

Study with cemiplimab: R2810-ONC-1624

R2810-ONC-1624 is an ongoing, open-label RCT on the comparison of cemiplimab with a platinum-based combination chemotherapy. The study included adult patients with histologically or cytologically confirmed stage IIIB, IIIC or IV NSCLC without EGFR mutation and without ALK translocation and ROS1 translocation, whose tumours had a PD-L1 expression ≥ 50%. Patients had to be in good general condition (corresponding to an Eastern Cooperative Oncology Group Performance Status [ECOG PS] ≤ 1) and were not allowed to have received prior systemic therapy for advanced or metastatic disease. In addition, definitive radiochemotherapy had to be unsuitable for the patients. Never smokers, defined as ≤ 100 cigarettes in their lives, were excluded from the study.

The study R2810-ONC-1624 included a total of 710 patients, assigned in a 1:1 ratio either to treatment with cemiplimab (N = 356) or with a platinum-based combination chemotherapy

(N = 354). The treatment options were as follows: pemetrexed + cisplatin, pemetrexed + carboplatin, paclitaxel + cisplatin, paclitaxel + carboplatin, gemcitabine + cisplatin or gemcitabine + carboplatin, whereby the combination with pemetrexed was only an option for patients with non-squamous histology. The choice of the platinum-based combination chemotherapy was determined by the investigator prior to randomization and was based on the regional guidelines or standard health care. Randomization was stratified by histology (non-squamous, squamous) and geographical region (Europe, Asia, rest of the world).

In the study, the PD-L1 expression of the tumour tissue was determined by means of immunohistochemistry using the 22C3 assay. However, prior to August 2018, PD-L1 expression testing was not performed according to the assay instructions. Therefore, the total population of the study also comprised patients whose tumour cells have a PD-L1 expression ≥ 50%. The company presented the results of a subpopulation that comprised the patients enrolled before August 2018, in whom PD-L1 expression of the tumours of ≥ 50 % was verified in a retest, as well as the patients included as of August 2018. The subpopulation formed by the company is relevant for the benefit assessment and comprises N = 283 patients in the intervention arm and N = 280 patients in the chemotherapy arm. However, the company presented results for this subpopulation only for the outcomes in the categories “mortality”, “morbidity” and “health-related quality of life”. For side effects, the company used the results of the safety population (n = 697). The approach of the company was not appropriate. The results of the relevant subpopulation are also required for the outcomes on side effects.

Administration of cemiplimab was in compliance with the requirements of the SPC [37]. Maximum treatment duration was 108 weeks. This treatment duration was achieved by 3 patients. The platinum-based combination chemotherapies (pemetrexed + cisplatin or carboplatin, paclitaxel + cisplatin or carboplatin, gemcitabine + cisplatin or carboplatin) were administered in accordance with the requirements of the respective SPCs [38-42]. The platinum component of the chemotherapy was administered for a maximum of 4 to 6 cycles in the R2810-ONC-1624 study. After at least 4 cycles, patients with non-squamous histology could receive maintenance treatment with pemetrexed. Information on how many patients with squamous histology received such maintenance treatment is not available.

Treatment was given until disease progression, occurrence of unacceptable toxicity, death or withdrawal of consent.

After disease progression and confirmed suitability, patients in the cemiplimab arm could be treated with cemiplimab in combination with platinum-based combination chemotherapy for a further 108 weeks (4 cycles). Patients in the comparator arm could switch to treatment with cemiplimab as monotherapy (up to 108 weeks). 107 (38.2%) patients had switched to treatment with cemiplimab by the relevant data cut-off of 1 March 2020. After the primary outcome “overall survival” had been reached at the time of the 9th protocol amendment (May 2020), patients in the comparator arm were allowed to switch to cemiplimab even before disease progression. However, cemiplimab is not approved for treatment after prior chemotherapy.

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

Studies with the ACT: KEYNOTE 024 and KEYNOTE 042

KEYNOTE 024

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

The KEYNOTE 024 study included a total of 305 patients, randomized in a 1:1 ratio either to treatment with pembrolizumab monotherapy (N = 154) or to one of 5 possible treatment options as platinum-based combination 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. The administration of pembrolizumab corresponds to the requirements of the SPC [43]. The maximum treatment duration for pembrolizumab was 35 cycles (105 weeks). In the KEYNOTE 024 study, no patient in the total study population reached this maximum treatment duration. The platinum-based combination chemotherapies (pemetrexed + cisplatin, pemetrexed + carboplatin, gemcitabine + cisplatin, gemcitabine + carboplatin, paclitaxel + carboplatin) were administered in accordance with the requirements of the respective SPCs [38-42]. 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. Overall, 46 (37%) of the patients with non-squamous histology in the comparator arm received such maintenance treatment.

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

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

KEYNOTE 042

As already described in the dossier assessments on the projects A19-30 and A19-31, KEYNOTE 042 is an ongoing, 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 with locally advanced or metastatic tumours with PD-L1 expression ≥ 1%. Prior systemic treatment was not allowed in the study. For patients who had received adjuvant or neoadjuvant therapy, treatment had to be terminated at least 6 months prior to the development of metastases. The ECOG-PS had to be 0 or 1 in the included patients. 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 considered for patients with non-squamous histology.

A total of 1274 patients were randomly allocated to the intervention arm (pembrolizumab: N = 637) or to the comparator arm (N = 637) in a 1:1 ratio. Randomization was stratified by ECOG PS (0, 1), histology (squamous, non-squamous), PD-L1 expression (≥ 50%, 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 with PD-L1 expression ≥ 50% (N = 599) are relevant for the benefit assessment. Data for the entire relevant subpopulation are only available from the publication Mok 2019 for the outcome "overall survival". The benefit assessment procedures 2019-04-01-D-447 + 2019-04-01-D-448 [35,36] provide further analyses, which are, however, limited to those patients for whom carboplatin represented a suitable treatment option according to a retrospective investigator survey carried out by the company for the procedures of the time in accordance with the specifications of the AM-RL on off-label use (Appendix VI to Section K [34]). These analyses are only available separately for patients with squamous (N = 176) and non- squamous histology (N = 120) and comprise just under 50% of the relevant subpopulation.

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). In the KEYNOTE 042 study, this maximum treatment duration was only reached by approx. < 7% of the patients in the total study population. The platinum-based combination chemotherapies (pemetrexed + carboplatin or paclitaxel + carboplatin) were also administered in accordance with the requirements of the SPC [40-42]. 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, patients with non-squamous histology could receive maintenance treatment with pemetrexed,

which was also recommended. 196 (52.3%) patients with non-squamous histology in the total population of the KEYNOTE 042 study received such maintenance treatment.

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

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

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

Molecular testing of the patients

No molecularly stratified therapy (against EGFR, ALK, BRAF or ROS1) could be considered for the patients at the time of treatment with cemiplimab. The S3 guideline [44] stipulates that molecular pathological examinations regarding all therapeutically relevant molecular changes (according to the current status before first-line treatment, EGFR mutations in exons 18-21, ALK fusions and ROS1 fusions, BRAF V600 mutations as a minimum requirement) are to be initiated on the basis of the available tumour tissue/tumour cells of all non-curatively treatable non-squamous NSCLC. This also applies to squamous cell carcinoma of never smokers/light smokers. According to the S3 guideline, targeted therapies are available for patients with the cited mutations or translocations [44].

In the R2810-ONC-1624 study, the tumour tissue of all patients was tested for EGFR mutations and ALK translocations as well as ROS1 translocations during screening. According to the study protocol, testing for BRAF V600 mutations was not mandated. It is therefore possible that the study included patients with non-squamous NSCLC who had BRAF V600 mutation. In the studies KEYNOTE 024 and KEYNOTE 042, patients with non-squamous NSCLC and unknown EGFR and/or ALK status had to be tested for this mutation or translocation before randomization into the 2 RCTs. However, in patients with squamous NSCLC and unknown EGFR and/or ALK status, testing was not required according to study protocols. Moreover, the respective study protocols do not indicate any planned screening or testing of the tumour tissue for ROS1 translocations or BRAF V600 mutations. It is therefore possible that the studies included patients with non-squamous NSCLC who had a ROS1 translocation or BRAF V600 mutation. It is also possible that never smokers or light smokers with squamous NSCLC who had an (unknown) EGFR mutation, ALK translocation, ROS1 translocation or BRAF V600 mutation were included.

Due to the rather rare occurrence of the individual mutations in the respective populations (non-squamous NSCLC/squamous NSCLC) and the smaller share of patients with squamous NSCLC in the individual studies, it is assumed that the number of included patients with the described

mutations or translocations was too small to call the similarity or relevance of the study populations into question.

Similarity of the common comparator platinum-based combination chemotherapy in the studies

For the present indirect comparison, the company chose "platinum-based combination chemotherapy" as common comparator. In the 3 included studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042, this includes different platinum-based combination chemotherapies. These differed between the studies: For example, paclitaxel was only a treatment option in combination with cisplatin on the cemiplimab side of the indirect comparison, and in the KEYNOTE 042 study, only carboplatin was administered as the platinum component (see also Table 7).

Table 8 shows which options of platinum-based combination chemotherapy were administered to the patients in the 3 studies.

Table 8: Distribution of the platinum-based combination chemotherapy regimens of the studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 (multipage table)

Study with cemiplimab	**Studies with pembrolizumab**	
R2810-ONC-1624 (N = 280)	**KEYNOTE 024 (N = 151)**	**KEYNOTE 042 (N = 300)**
Non-squamous histology		
n = 159 (57%)[a]	**n = 124 (82%)**	**n = 186 (62%)**
Pemetrexed + ▪ cisplatin: ND for the relevant subpopulation ▪ carboplatin: ND for the relevant subpopulation maintenance treatment with pemetrexed: ND for the relevant subpopulation gemcitabine + ▪ cisplatin: ND for the relevant subpopulation ▪ carboplatin: ND for the relevant subpopulation paclitaxel + ▪ cisplatin: ND for the relevant subpopulation ▪ carboplatin: ND for the relevant subpopulation	Pemetrexed + ▪ cisplatin: 36 (29%) ▪ carboplatin: 66 (54%) maintenance treatment with pemetrexed: 46 (30%)[b] gemcitabine + ▪ cisplatin: 4 (3%) ▪ carboplatin: 5 (4%) paclitaxel + carboplatin: 12 (10%)	Pemetrexed + carboplatin: ND for the relevant subpopulation paclitaxel + carboplatin: ND for the relevant subpopulation maintenance treatment with pemetrexed: ND for the relevant subpopulation
Squamous histology		
n = 121 (43%)[a]	**n = 27 (18%)**	**n = 114 (38%)**
Gemcitabine + ▪ cisplatin: ND for the relevant subpopulation carboplatin: ND for the relevant subpopulation paclitaxel + ▪ cisplatin: ND for the relevant subpopulation ▪ carboplatin: ND for the relevant subpopulation	Gemcitabine + ▪ cisplatin: 7 (26%) ▪ carboplatin: 15 (56%) paclitaxel + carboplatin: 5 (19%)	Paclitaxel + carboplatin: 114 (100%)
Total[b]		
▪ Cisplatin: ND for the relevant subpopulation ▪ carboplatin: ND for the relevant subpopulation	▪ Cisplatin: 47 (31%) ▪ carboplatin: 103 (68%)	Carboplatin: 300 (100%)

Table 8: Distribution of the platinum-based combination chemotherapy regimens of the studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 (multipage table)

Study with cemiplimab	Studies with pembrolizumab	
R2810-ONC-1624 (N = 280)	**KEYNOTE 024 (N = 151)**	**KEYNOTE 042 (N = 300)**
a. No data on patients in the relevant subpopulation; distribution in the entire control group of the safety population (N = 342): pemetrexed + carboplatin (n = 99 [29%]), pemetrexed + cisplatin (n = 38 [11%]), paclitaxel + carboplatin (n = 124 [36%]), paclitaxel + cisplatin (n = 10 [3%]), gemcitabine + carboplatin (n = 37 [11%]) and gemcitabine + cisplatin (n = 34 [10%]). b. No data on patients in the relevant subpopulation; distribution in the entire control group of the safety population (N = 342): cisplatin (n = 82 [24%]) and carboplatin (n = 260 [76%]); Institute's calculation. c. Institute's calculation, percentages related to the entire control group N = 151 n: patients with respective histology; N: number of randomized patients in the (relevant) (sub)populations; ND: no data		

Dossier assessment A17-06 [14] provides detailed information on the administered platinum-based combination chemotherapies for the KEYNOTE 024 study. There is hardly any information on the administered platinum-based combination chemotherapies for each of the relevant subpopulations of the studies R2810-ONC-1624 and KEYNOTE 042. For the R2810-ONC-1624 study, only data on the comparator arm of the safety population are available, however, this arm also includes patients with a PD-L1 status < 50%.

Platinum component of the common comparator

In R2810-ONC-1624, the platinum-based combination chemotherapy was chosen prior to randomization at the discretion of the investigator and had to comply with the local treatment standard. There is no information on possible selection criteria of the platinum components in the studies KEYNOTE 024 and KEYNOTE 042; in each case, there is only the information that the choice took place on an individual basis prior to randomization.

For study R2810-ONC-1624, no information is available on the distribution of the platinum component in the relevant subpopulation (see Table 8). In the safety population of the R2810-ONC-1624 study, approximately one quarter of the patients in the comparator arm received cisplatin, and the remaining patients received carboplatin. About 1 third of the patients in the comparator arm of the KEYNOTE 024 study received cisplatin, and the remaining patients received carboplatin. In the KEYNOTE 042 study, only carboplatin was administered.

As described above, the present analyses from the KEYNOTE 042 study (except for the outcome “overall survival”) only include just under 50% of the relevant subpopulation, as this was restricted post hoc 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 the off-label use (Appendix VI to Section K [34]). The company did not make such a restriction of the population for the studies R2810-ONC-1624 and KEYNOTE 024.

Chemotherapy component of the common comparator

In the R2810-ONC-1624 study, patients could receive pemetrexed (only in case of non-squamous histology), gemcitabine as well as paclitaxel, each in combination with cisplatin or carboplatin. Deviating from this, paclitaxel in combination with cisplatin was no treatment option in the KEYNOTE 024 study nor in the KEYNOTE 042 study. Moreover, patients in KEYNOTE 042 could not be treated with gemcitabine.

More than 80% of the patients with non-squamous NSCLC received pemetrexed in the KEYNOTE 024 study. There is no information for the relevant subpopulation of the studies R2810-ONC-1624 and KEYNOTE 042. 70% of the 196 patients with non-squamous NSCLC of the safety population of R2810-ONC-1624 received pemetrexed.

In the KEYNOTE 024 study, 81% of the patients with squamous histology received gemcitabine in addition to the platinum component; the remaining patients received paclitaxel. In the KEYNOTE 042 study, only paclitaxel could be administered in addition to carboplatin. There is no information for the relevant subpopulation of the R2810-ONC-1624 study.

In the comparator arm of the KEYNOTE 024 study, a total of 11% of the patients (with squamous and non-squamous histology), and at least 38% of the patients in KEYNOTE 042 received paclitaxel; concrete information is not available. There is no information for the relevant subpopulation of the R2810-ONC-1624 study either. In the safety population of the R2810-ONC-1624 study, about 40% of the patients (with squamous and non-squamous histology) in the comparator arm were treated with paclitaxel.

Maintenance treatment in the common comparator

In the KEYNOTE 024 study, 37% of the patients with non-squamous histology received maintenance therapy with pemetrexed, although this maintenance therapy was recommended according to the study documents. In the studies R2810-ONC-1624 and KEYNOTE 042, administration of a maintenance treatment was at the investigator's discretion and was recommended in the KEYNOTE 042 study. There is no information for the relevant subpopulation of the two studies.

Summary

Data on the proportions of each platinum-based combination chemotherapy received in the comparator arm of the relevant subpopulation are missing, in particular, for the R2810-ONC-1624 study. Therefore, the similarity of the common comparators cannot be assessed with sufficient certainty.

Moreover, it must be assumed that the KEYNOTE 042 study differs relevantly from the studies R2810-ONC-1624 and KEYNOTE 024 with regard to the study population in the common comparator due to the post hoc restriction of the subpopulation to those patients for whom, according to a retrospective survey, carboplatin presents a suitable treatment option in accordance with the AM-RL for the off-label use (Appendix VI to Section K, [34]).

Planned duration of follow-up observation

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

Table 9: Planned duration of follow-up observation – RCT, indirect comparison: cemiplimab vs. pembrolizumab (multipage table)

Study **outcome category** **outcome**	**Planned follow-up observation**
Cemiplimab vs. platinum-based combination chemotherapy	
R2810-ONC-1624	
Mortality	
Overall survival	Until death, lost to follow-up, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-LC13)	Until 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	Until 30 days after the last visit
Side effects	
All outcomes in the category of side effects	Until 90 days after the last dose of the study medication or until start of a new antineoplastic treatment
Pembrolizumab vs. platinum-based combination chemotherapy	
KEYNOTE 024	
Mortality	
Overall survival	Until death
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-LC13) health status (EQ-5D VAS)	▪ Until 30 days after the last dose of the study medication ▪ at treatment discontinuation before progression: until progression or initiation of new antineoplastic treatment
Health-related quality of life (EORTC QLQ-C30)	▪ Until 30 days after the last dose of the study medication ▪ at treatment discontinuation before progression: until progression or initiation of new antineoplastic treatment
Side effects	
AEs	Until 30 days after the last dose of the study medication
SAEs and immune-related AEs	Until 90 days after the last dose of the study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment was initiated, whichever occurred first)

Table 9: Planned duration of follow-up observation – RCT, indirect comparison: cemiplimab vs. pembrolizumab (multipage table)

Study **outcome category** **outcome**	**Planned follow-up observation**
KEYNOTE 042	
Mortality	
Overall survival	Until death
Morbidity	Not recorded
Health-related quality of life	Not recorded
Side effects	
AEs	Until 30 days after the last dose of the study medication or until initiation of a new antineoplastic treatment (whichever occurred first)
SAEs and immune-related AEs	Until 90 days after the last dose of the study medication (or until 30 days after the last dose of the study medication if new antineoplastic treatment was initiated, whichever occurred first)

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

In all 3 studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042, the observation periods for the outcomes "morbidity", "health-related quality of life" and "side effects" were systematically shortened, as they were only recorded for the period of treatment with the study medication (plus 30 days or plus 90 days for SAEs and immune-related AEs [in the case of R2910-ONC-1624 also for AEs]). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Patient characteristics

Table 10 shows the characteristics of the patients in the studies included.

Table 10: Characteristics of the study population – RCT, indirect comparison: cemiplimab vs. pembrolizumab (multipage table)

Study characteristic category	Cemiplimab vs. platinum-based combination chemotherapy		Pembrolizumab vs. platinum-based combination chemotherapy			
	R2810-ONC-1624		KEYNOTE 024		KEYNOTE 042	
	cemiplimab	platinum-based combination chemotherapy	pembrolizumab	platinum-based combination chemotherapy	pembrolizumab	platinum-based combination chemotherapy
	N[a] = 283	N[a] = 280	N = 154	N = 151	N = 299	N = 300
Age [years], mean (SD)	63 (8)	64 (8)	64 (10)	65 (10)	65 [33; 90][b]	66 [38; 85][b]
Sex [F/M], %	12/88	17/83	40/60	37/63	31/69	30/70
Family origin, n (%)						
White	243 (86)	240 (86)	125 (81)	126 (83)	ND	ND
Non-white	40 (14)[c]	40 (14)[c]	27 (18[d])	25 (17)	ND	ND
Unknown	0 (0)	0 (0)	2 (1)	0 (0)	ND	ND
Region, n (%)						
Europe	215 (76)	216 (77)	ND	ND	71 (24)	66 (22)
Rest of the world	68 (24)[d,e]	64 (23)[d,e]	ND	ND	228 (76)[d]	234 (78)[d]
Smoking status, n (%)						
Never-smoker	0 (0)	0 (0)	5 (3)	19 (13)	64 (21)	67 (22)
Active	105 (37)	92 (33)	34 (22)	31 (21)	57 (19)	59 (20)
Former	178 (63)	188 (67)	115 (75)	101 (67)	178 (60)	174 (58)
ECOG PS, n (%)						
0	77 (27)	75 (27)	54 (35)	53 (35)	96 (32)	91 (30)
1	206 (73)	205 (73)	99 (64)	98 (65)	203 (68)	209 (70)
Unknown	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Disease stage, n (%)						
IIIB	36 (13)	33 (12)	1 (1)	1 (1)	ND[f]	ND[f]
IIIC	9 (3)	9 (3)	–	–	–	–
IV	238 (84)	238 (85)	153 (99)	150 (99)	ND	ND

Table 10: Characteristics of the study population – RCT, indirect comparison: cemiplimab vs. pembrolizumab (multipage table)

Study characteristic category	Cemiplimab vs. platinum-based combination chemotherapy		Pembrolizumab vs. platinum-based combination chemotherapy			
	R2810-ONC-1624		KEYNOTE 024		KEYNOTE 042	
	cemiplimab	platinum-based combination chemotherapy	pembrolizumab	platinum-based combination chemotherapy	pembrolizumab	platinum-based combination chemotherapy
	N[a] = 283	N[a] = 280	N = 154	N = 151	N = 299	N = 300
Metastasis, n (%)						
M0	45 (16)	42 (15)	1 (1)	1 (1)	ND	ND
M1	15 (5)	9 (3)	29 (19)	34 (23)	ND	ND
M1A	65 (23)	67 (24)	47 (31)	41 (27)	ND	ND
M1B	76 (27)	80 (29)	77 (50)	74 (49)	ND	ND
M1C	82 (29)	82 (29)	–	–	ND	ND
MX	–	–	0 (0)	1 (1)	ND	ND
Time since initial diagnosis [months]						
Mean (SD)	3.1 (7.5)	4.5 (17.1)	5.7 (13.4)	6.2 (23.7)	ND	ND
Median [min; max]	1.7 [0.5; 92.7]	1.8 [0.5; 263.8]	1.7 [0.7; 114.8]	1.7 [0.5; 230.8]	ND	ND
Tumour size at baseline [mm]						
Mean (SD)	ND	ND	90.9 (53.4)	99.8 (63.4)	ND	ND
Median [min; max]	ND	ND	82.0 [14.0; 322.0]	83.5 [14.0; 369.0]	ND	ND
Brain metastases, n (%)						
Yes	34 (12)	34 (12)	18 (12)	10 (7)	19 (6)	15 (5)
No	249 (88)	246 (88)	136 (88)	141 (93)	280 (94)	284 (95)
Histology, n (%)						
Squamous	122 (43)	121 (43)	29 (19)	27 (18)	107 (36)	114 (38)
Non-squamous	161 (57)	159 (57)	125 (81)	124 (82)	192 (64)	186 (62)

Table 10: Characteristics of the study population – RCT, indirect comparison: cemiplimab vs. pembrolizumab (multipage table)

Study characteristic category	Cemiplimab vs. platinum-based combination chemotherapy		Pembrolizumab vs. platinum-based combination chemotherapy			
	R2810-ONC-1624		KEYNOTE 024		KEYNOTE 042	
	cemiplimab	platinum-based combination chemotherapy	pembrolizumab	platinum-based combination chemotherapy	pembrolizumab	platinum-based combination chemotherapy
	N[a] = 283	N[a] = 280	N = 154	N = 151	N = 299	N = 300
Prior therapies, n (%)						
Adjuvant prior therapy	5 (2)	12 (4)	6 (4)	3 (2)	8 (3)[g]	4 (1)[g]
Neoadjuvant prior therapy	3 (1)	4 (1)	3 (2)	1 (1)	1 (< 1)[g]	5 (2)[g]
Platinum-based chemotherapy, n (%)						
Cisplatin	NA	ND[h]	NA	47 (31)	NA	0 (0)
Carboplatin	NA	ND[h]	NA	103 (68)	NA	300 (100)
Treatment discontinuation, n (%)	148 (52)	110 (39)	80 (52[d])	106 (70[d])	217 (73[d])	194 (65[d])
Study discontinuation, n (%)	ND	ND	47 (31)[d]	69 (46)[d]	ND	ND

a. Subpopulation of randomized patients in whom the PD-L1 expression ≥ 50% was verified in a retest.
b. Median [min; max].
c. Summary: "black or African American", "Asian", "Native Indian or Native Alaskan" and "other".
d. Institute's calculation.
e. Rest of the world included Asia with 31 (in the cemiplimab arm) or 29 (in the comparator arm) patients.
f. Data only available for locally advanced: 27 (9%) in the pembrolizumab arm and 35 (12%) in the chemotherapy arm, or metastatic: 272 (91%) in the pembrolizumab arm versus 265 (88%) in the chemotherapy arm.
g. Prior therapy for non-metastatic disease.
h. No data on patients in the relevant subpopulation; distribution in the entire control group of the safety population (N = 342): cisplatin (n = 82 [24 %]) and carboplatin (n = 260 [76 %]); Institute's calculation.

ECOG: Eastern Cooperative Oncology Group; F: female; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; NA: not applicable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

Information on the interesting patient characteristics are not available for all 3 studies. However, based on the available information, the populations can be assessed as sufficiently comparable both between the R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 studies and between the treatment arms in each of the individual studies. The mean age of the patients included in the studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 was 65 years, most of them were male and white (information on the family origin were not available for the KEYNOTE 024 study). The majority of patients in the 3 studies had not brain metastases. While in the studies R2810-ONC-1624 and KEYNOTE 042 about 40% of the patients had squamous cell NSCLC, in the KEYNOTE 024 study it was only just under 20%. The remaining patients had non-squamous NSCLC.

Treatment duration and observation period

Table 11 shows the mean and median treatment durations of the patients and the mean/median observation periods for individual outcomes.

Table 11: Information on the course of the study – RCT, indirect comparison: cemiplimab vs. pembrolizumab

Study **duration of the study phase** **outcome category**	**Cemiplimab or pembrolizumab**	**Platinum-based combination chemotherapy**
Cemiplimab vs. platinum-based combination chemotherapy		
R2810-ONC-1624 (data cut-off 1 March 2020)	**N = 283**	**N = 280**
Treatment duration [months]		
Median [min; max]	6.2[a] [ND]	4.1[a] [ND]
Mean (SD)	ND	ND
Observation period [months]	ND	ND
Pembrolizumab vs. platinum-based combination chemotherapy		
KEYNOTE 024 (data cut-off 6 May 2016)	**N = 154**	**N = 150**
Treatment duration [months]		
Median [min; max]	7.0 [0.0; 18.7]	3.5 [0.0; 16.8]
Mean (SD)	6.8 (4.8)	4.0 (3.5)
Observation period [months]	ND	ND
KEYNOTE 042 (data cut-off 26 February 2018)	**N = 299**	**N = 300**
Treatment duration [months]	ND	ND
Observation period [months]	ND	ND

a. Institute's calculation.

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

For the studies R2810-ONC-1624 and KEYNOTE 024, information is only available for the treatment duration. The median treatment duration was comparable between the studies and

was about 1.5 to 2 times longer in the intervention arm than in the comparison arm. The observation period for side effects in the studies R2810-ONC-1624 and KEYNOTE 024 can be estimated from the data on median treatment duration, as the recording of AEs was planned for 90 (R2810-ONC-1624) and 30 days (KEYNOTE 024), and for SAEs for 90 days after the last study medication. For the KEYNOTE 042 study, information was neither available for the treatment duration nor for the observation period. The similarity of the studies in terms of treatment durations and observation periods cannot be assessed due to the lack of information.

Subsequent therapies

Table 12 shows, which subsequent therapies patients received after discontinuing the study medication.

Table 12: Information on subsequent antineoplastic therapies – RCT, indirect comparison: cemiplimab vs. pembrolizumab:

Study drug	Patients with subsequent therapy n (%)	
	cemiplimab or pembrolizumab	platinum-based combination chemotherapy
Cemiplimab vs. platinum-based combination chemotherapy		
R2810-ONC-1624 (data cut-off 1 March 2020)	**N = 283**	**N = 280**
Total	60 (21.2)	113 (40.4)
Surgery	0 (0)	1 (0.4)
Systemic therapy	60 (21.2)	112 (40.0)
Switch to cemiplimab	NA	107 (38.2)
Cemiplimab + chemotherapy as extension therapy	46 (16.3)	0 (0)
Carboplatin	9 (3.2)	7 (2.5)
Paclitaxel	6 (2.1)	4 (1.4)
cisplatin	5 (1.8)	1 (0.4)
Pemetrexed	4 (1.4)	0 (0)
Docetaxel	2 (0.7)	0 (0)
Gemcitabine	2 (0.7)	2 (0.7)
Vinorelbine	2 (0.7)	1 (0.4)
Afatinib	1 (0.4)	0 (0)
Bevacizumab	1 (0.4)	0 (0)
Etoposide	1 (0.4)	3 (1.1)
Nintedanib esilate	1 (0.4)	0 (0)
Pembrolizumab	0 (0)	2 (0.7)
Pembrolizumab vs. platinum-based combination chemotherapy		
KEYNOTE 024 (data cut-off 9 May 2016)	**N = 154**	**N = 151**
Total	35 (22.7)	91 (60.3)[a]
Switch to pembrolizumab	NA	66 (43.7)
KEYNOTE 042 (data cut-off 26 February 2018)	**N = 299**	**N = 300**
Total	ND[b]	ND[b]
Switch to pembrolizumab	NA	ND[b]

a. Institute's calculation.
b. No data for the relevant subpopulation: the proportion of patients with antineoplastic subsequent therapy in the entire subpopulation was 37.7% (N = 240) in the intervention arm and 44.0% (N = 280) in the comparator arm. In the comparator arm, 28 (4.4%) patients had switched to monotherapy with pembrolizumab.

n: number of patients with subsequent therapy; N: number of analysed patients; NA: not applicable; RCT: randomized controlled trial

In R2810-ONC-1624, 60 (21.2%) patients in the intervention arm and 113 (40.4%) patients in the comparator arm received subsequent therapy. In the intervention arm, 46 (16.3%) patients were treated with cemiplimab in combination with 4 cycles of a histology-specific chemotherapy. 107 (38.2%) patients in the comparator arm switched to treatment with cemiplimab. However, cemiplimab is not approved for treatment after prior chemotherapy.

At the time point of the second interim analysis of 9 May 2016, 35 (22.7%) patients in the intervention arm and 91 (60.3%) in the comparator arm of the KEYNOTE 024 study received subsequent therapy. Of these, 66 (43.7%) patients in the comparator arm switched to monotherapy with pembrolizumab.

No information on concrete subsequent therapies in the relevant subpopulation was available for the KEYNOTE 042 study. At the time point of the data cut-off of 26 February 2018, the proportion of patients with antineoplastic subsequent therapy in the entire subpopulation was 37.7% (N = 240) in the intervention arm and 44.0% (N = 280) in the comparator arm. In the comparator arm, 28 (4.4%) patients had switched to monotherapy with pembrolizumab.

The similarity of the studies in terms of subsequent therapies cannot be sufficiently assessed due to incomplete data.

2.3.3 Usability of the indirect comparison presented by the company

Similarity of the studies and usability of the analyses presented by the company in the adjusted indirect comparison

Similarity is a key requirement for the consideration of studies in the adjusted indirect comparison. Basically, the 3 studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 have a very similar study design and the patient populations are also sufficiently similar. However, certain aspects cannot be assessed with sufficient certainty due to missing information (especially on the therapies in the comparator arm of study R2810-ONC-1624). Moreover, it must be assumed that the KEYNOTE 042 study differs relevantly from the studies R2810-ONC-1624 and KEYNOTE 024 with regard to the study population in the common comparator due to the post hoc restriction of the subpopulation to those patients for whom, according to a retrospective survey, carboplatin presents a suitable treatment option in accordance with the AM-RL for the off-label use (Appendix VI to Section K, [34]).

Moreover, the results of the 3 studies R2810-ONC-1624, KEYNOTE 024 and KEYNOTE 042 were not adequately prepared. The separate indirect comparisons presented by the company are not usable for the benefit assessment (see Section 2.3.1). At first, a meta-analytical summary of the studies KEYNOTE 024 and KEYNOTE 042 is required, followed by an indirect comparison with the R2810-ONC-1624 study.

Further notes on the data presented by the company

At the time point of the relevant data cut-off, 107 (approx. 38%) of the patients in the comparator arm of the study R2810-ONC-1624 were receiving cemiplimab as subsequent

therapy. This is no approved treatment option after prior chemotherapy [37]. This would result in a high risk of bias in the results on “overall survival”. It is unclear which data are considered in the analysis of the outcome "overall survival”. In the section on the risk of bias at study level of Module 4 B, the company states that the results on the relevant data cut-off only take into account the data from the two study arms before the treatment switch. However, the operationalization of the outcome provides no information on a censoring of patients from the comparator arm who received cemiplimab as subsequent therapy. Even if these patients had been censored in the analysis of the outcome “overall survival”, the risk of bias would be high due to the large proportion of informative censorings. Regardless of this, there is no statistically significant difference between the treatment arms for the outcome “overall survival” in any of the indirect comparisons presented by the company.

For the study R2810-ONC-1624, the company only presented analyses on AEs for the safety population and not for the relevant subpopulation. As the relevant subpopulation is less than 80% of the total study population, analyses of the indirect comparison under consideration of the relevant subpopulation would be required. In addition, the data on frequent AEs provided by the company for the safety population do not meet the requirements of the dossier templates. For example, the company presents severe AEs (CTCAE grade ≥ 3) with an incidence of ≥ 10% in at least one study arm; results on frequent AEs are missing. According to the dossier template, however, all events that occurred in ≥ 10 patients and in ≥ 1% of the patients in a study arm must also be reported for serious AEs and SAEs.

2.4 Results on added benefit

The data presented by the company for the assessment of the added benefit of cemiplimab in the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive radiochemotherapy, or adult patients with metastatic NSCLC whose tumours express PD-L1 in ≥ 50% of the tumour cells and who have no EGFR, ALK or ROS1 aberrations, are not suitable for deriving an added benefit of cemiplimab compared with the ACT. This resulted in no hint of an added benefit of cemiplimab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

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

The result of the assessment of the added benefit of cemiplimab in comparison with the ACT is summarized in Table 13.

Table 13: Cemiplimab – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
First-line treatment of adult patients with NSCLC whose tumours express PD-L1 in ≥ 50% of the tumour cells and have no aberrations due to EGFR, ALK or ROS1. Treatment is intended for: ▪ patients with locally advanced NSCLC who are not candidates for definite radiochemotherapy, or ▪ patients with metastatic NSCLC	Pembrolizumab[c] as monotherapy	Added benefit not proven

a. For the patients covered by the present field of application, it is assumed that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy.
b. Presentation of the respective ACT specified by the G-BA.
c. In the present therapeutic indication, pembrolizumab is approved as monotherapy only for patients with metastatic NSCLC.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; ROS1: c-ros oncogene 1

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit on the basis of the indirect comparison with the studies R2810-ONC-1624 for cemiplimab and KEYNOTE 024 for pembrolizumab and the indirect comparison of the subpopulations with non-squamous histology of the studies R2810-ONC-1624 for cemiplimab and KEYNOTE 042 for pembrolizumab analysed by it.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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