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Ipilimumab (NSCLC) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ipilimumab (NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 March 2021). 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
AM-RL	Arzneimittel-Richtlinie (Pharmaceutical Directive)
ASBI	average symptom burden index
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCSS	Lung Cancer Symptom Scale
MMRM	mixed-effects model with repeated measures
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PT	Preferred Term
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TPS	Tumour Proportion Score
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ipilimumab. 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 14 December 2020.

Research question

The aim of the present report is the assessment of the added benefit of ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy (hereinafter referred to as "ipilimumab + nivolumab + platinum-based chemotherapy") in comparison with the appropriate comparator therapy (ACT) as first-line treatment in adult patients with metastatic non-small cell lung cancer (NSCLC) without sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation.

The G-BA's specification of the ACT resulted in 2 research questions, which are presented in the following Table 2.

Table 2: Research questions of the benefit assessment of ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy

Research question	Subindication	ACT[a]
1	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) ≥ 50%[b]	Pembrolizumab as monotherapy
2	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]) *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]); see Appendix VI to Section K of the Pharmaceutical Directive *or* ▪ carboplatin in combination with nab-paclitaxel *or* ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) *or* ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.

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

The company followed the G-BA's specification of the ACT for both research questions, and chose a platinum-based chemotherapy (cisplatin or carboplatin in combination with a third-generation cytostatic agent) for research question 2 from the options presented. The company assumed equivalence of the platinum components (carboplatin or cisplatin), however. This disregarded the G-BA's specification that the choice of the platinum component in each case should be based on the different toxicity profiles of the 2 substances and on the existing comorbidities (see Appendix VI to Section K of the Pharmaceutical Directive [AM-RL]). The present benefit assessment takes into account the restriction defined by the G-BA.

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

Results for research question 1: PD-L1 expression ≥ 50%

The company presented no data for the assessment of the added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT as first-line treatment in adult patients with metastatic NSCLC without sensitizing EGFR mutation or ALK translocation and programmed cell death ligand 1 (PD-L1) expression ≥ 50%. This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT; an added benefit for this research question is therefore not proven.

Results for research question 2: PD-L1 expression < 50%

Study pool

One relevant study (CA209-9LA) was available for the benefit assessment.

The specification of the research question (patients with PD-L1 expression < 50%) and of the ACT (choice of the platinum component) resulted in restrictions that only apply to a subpopulation of the CA209-9LA study. This is explained in more detail in the following section.

Study characteristics

The CA209-9LA study is an ongoing, open-label, multicentre RCT comparing ipilimumab + nivolumab + platinum-based chemotherapy (hereinafter referred to as "intervention arm") with platinum-based chemotherapy (hereinafter referred to as "comparator arm").

The study included adult patients with squamous and non-squamous stage IV NSCLC without EGFR mutation or ALK translocation and Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 irrespective of the PD-L1 expression. The inclusion criteria of the CA209-9LA study additionally comprised patients with stage IIIB disease without the option of curative therapy. Patients with untreated brain metastases were excluded from the study. No prior systemic therapy of the stage IIIB or IV NSCLC was allowed.

The CA209-9LA study included a total of 719 patients, randomized in a 1:1 ratio either to treatment with ipilimumab + nivolumab + platinum-based chemotherapy (N = 361) or to treatment with platinum-based chemotherapy alone (N = 358). The type of chemotherapy was dependent on the histology of the tumour: Patients with squamous histology received carboplatin in combination with paclitaxel. Patients with non-squamous histology received either cisplatin or carboplatin in combination with pemetrexed. The platinum component was chosen by the investigator before randomization on the basis of eligibility criteria not described in more detail by the company. Only the subpopulation of patients with non-squamous histology is relevant for the present research question (see below for explanations regarding the relevant subpopulation).

The therapy with ipilimumab as well as nivolumab complied with the requirements of the respective Summary of Product Characteristics (SPC). The maximum treatment duration for ipilimumab + nivolumab is 24 months. In both treatment arms, the use of platinum-based chemotherapy for patients with non-squamous histology and PD-L1 expression < 50% also complied with the recommendations of the guideline and the requirements of the SPC or the AM-RL for the off-label use of carboplatin in the therapeutic indication of NSCLC (Appendix VI to Section K of the AM-RL) (see below). In the comparator arm, up to 4 cycles of chemotherapy were administered; then patients with non-squamous histology and no disease progression could receive maintenance therapy with pemetrexed from cycle 5.

Treatment was given until disease progression, unacceptable intolerance, withdrawal of consent or reaching the maximum duration of therapy. Switching patients from the comparator arm to treatment with ipilimumab + nivolumab after disease progression was not permitted. There were no restrictions regarding subsequent therapies.

Primary outcome of the CA209-9LA study was overall survival. Secondary patient-relevant outcomes were recorded in the categories of morbidity and side effects.

The preplanned final analysis of the CA209-9LA study of 9 March 2020 was used for the benefit assessment.

Relevant subpopulation of the CA209-9LA study

PD-L1 status

Only the subpopulation of patients with metastatic NSCLC whose tumours have a PD-L1 expression < 50% (N = 497) is relevant for the present research question.

Implementation of the Pharmaceutical Directive on the use of carboplatin

Carboplatin is only approved in combination with nab-paclitaxel for the therapy of NSCLC in first-line treatment, but not in combination with other third-generation cytostatic agents. According to the current version of Appendix VI to Section K of the AM-RL, carboplatin can be prescribed in off-label use for patients with advanced NSCLC. In each case, the choice of the platinum component (carboplatin or cisplatin) should be based on the different toxicity profiles of the 2 substances and on the existing comorbidities. In the CA209-9LA study, treatment with carboplatin was not explicitly restricted according to these criteria. The choice of chemotherapy was based on the histology of the tumour. All patients with squamous histology received therapy with carboplatin. A choice of the platinum component based on the different toxicity profiles and existing comorbidities was not planned. The criteria of the AM-RL were not implemented for patients with squamous histology. The treatment of patients with squamous histology therefore did not correspond to the ACT specified by the G-BA.

For patients with non-squamous histology, the investigator could choose between treatment with carboplatin or cisplatin on a patient-specific basis before randomization. However, therapy with cisplatin was only possible if the patients fulfilled predefined eligibility criteria. Assuming

that the eligibility criteria for therapy with cisplatin defined in the study protocol were based on the recommendations of German and international guidelines, the choice of the platinum component in the CA209-9LA study is considered to be a sufficient implementation of the AM-RL and thus the ACT for research question 2, despite uncertainties.

Summary

The results of the subpopulation of patients with metastatic non-squamous NSCLC whose tumours have a PD-L1 expression < 50% were used in the present benefit assessment.

Thus, no usable data were available for patients with squamous NSCLC.

Risk of bias

The risk of bias across outcomes (study level) was rated as low for the CA209-9LA study. The outcome-specific risk of bias was rated as low for the outcome "overall survival" and as high for all other outcomes for which usable data were available.

Mortality

Overall survival

For the outcome "overall survival", there was a statistically significant effect in favour of ipilimumab + nivolumab + platinum-based chemotherapy for the relevant subpopulation. This resulted in an indication of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

Morbidity

Symptoms (LCSS ASBI)

For the outcome "Lung Cancer Symptom Scale average symptom burden index (LCSS ASBI)", no usable analyses were available for the relevant subpopulation. This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

For the outcome "European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS)", no usable analyses were available for the relevant subpopulation. This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Health-related quality of life

The CA209-9LA study did not record health-related quality of life. This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome "serious adverse events (SAEs)", there was a statistically significant difference to the disadvantage of ipilimumab + nivolumab + platinum-based chemotherapy for the relevant subpopulation. This resulted in a hint of greater harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

Severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment groups for the outcome "severe adverse events (AEs) (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" for the relevant subpopulation. This resulted in no hint of greater or lesser harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", no usable analyses were available for the relevant subpopulation. This resulted in no hint of greater or lesser harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

Immune-related AEs (AEs, SAEs and severe AEs) and further specific AEs

For immune-related AEs (AEs, SAEs and severe AEs) and further specific AEs, no usable analyses were available for the relevant subpopulation. This resulted in no hint of greater or lesser harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

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

On the basis of the results presented, probability and extent of the added benefit of the drug ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT are assessed as follows:

Research question 1: PD-L1 expression ≥ 50%

The company presented no data for the assessment of the added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT as first-line treatment

[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].

in adult patients with metastatic NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression ≥ 50%. An added benefit of ipilimumab + nivolumab + platinum-based chemotherapy is therefore not proven for research question 1.

Research question 2: PD-L1 expression < 50%

Patients with non-squamous histology

The overall picture shows one positive and one negative effect of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the relevant subpopulation. On the side of positive effects, there is an indication of a major added benefit for the outcome "overall survival". On the side of negative effects, on the other hand, there is a hint of greater harm with the extent "considerable" for the outcome "SAEs". Overall, the negative effect in SAEs does not call into question the positive effect in overall survival. However, as no usable data are available for symptom outcomes (LCSS), health status (EQ-5D VAS), discontinuation due to AEs, immune-related AEs and further specific AEs, the overall extent of the added benefit is non-quantifiable.

In summary, there is an indication of a non-quantifiable added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT for patients with metastatic non-squamous NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50% in first-line treatment.

Patients with squamous histology

No relevant data are available for patients with metastatic squamous NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50% in first-line treatment. The added benefit is not proven for this patient group.

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

Table 3: Ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) ≥ 50%[b]	Pembrolizumab as monotherapy	Added benefit not proven
2	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]) *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]); see Appendix VI to Section K of the Pharmaceutical Directive *or* ▪ carboplatin in combination with nab-paclitaxel *or* ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) *or* ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)	▪ Non-squamous histology: ▫ indication of an added benefit; extent "non-quantifiable"[c] ▪ Squamous histology: ▫ added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-9LA study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TPS: Tumour Proportion Score

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy (hereinafter referred to as "ipilimumab + nivolumab + platinum-based chemotherapy") in comparison with the ACT as first-line treatment in adult patients with metastatic NSCLC without sensitizing EGFR mutation or ALK translocation.

The G-BA's specification of the ACT resulted in 2 research questions, which are presented in the following Table 4.

Table 4: Research questions of the benefit assessment of ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy

Research question	Subindication	ACT[a]
1	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) ≥ 50%[b]	Pembrolizumab as monotherapy
2	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]) *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]); see Appendix VI to Section K of the Pharmaceutical Directive *or* ▪ carboplatin in combination with nab-paclitaxel *or* ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) *or* ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.

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

The company followed the G-BA's specification of the ACT for both research questions, and chose a platinum-based chemotherapy (cisplatin or carboplatin in combination with a third-generation cytostatic agent) for research question 2 from the options presented. The company assumed equivalence of the platinum components (carboplatin or cisplatin), however. The company disregarded the G-BA's specification that the choice of the platinum component in each case should be based on the different toxicity profiles of the 2 substances and on the existing comorbidities (see Appendix VI to Section K of the AM-RL [3]). The present benefit assessment takes into account the restriction defined by the G-BA.

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

2.3 Research question 1: PD-L1 expression ≥ 50%

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ipilimumab + nivolumab (status: 5 October 2020)
- bibliographical literature search on ipilimumab + nivolumab (last search on 1 October 2020)
- search in trial registries/trial results databases for studies on ipilimumab + nivolumab (last search on 5 October 2020)
- search on the G-BA website for ipilimumab + nivolumab (last search on 5 October 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ipilimumab + nivolumab (last search on 15 December 2020)

No relevant study was identified from the check. The company also identified no suitable studies.

2.3.2 Results on added benefit

The company presented no data for the assessment of the added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT as first-line treatment in adult patients with metastatic NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression ≥ 50%. This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT; an added benefit for this research question is therefore not proven.

2.3.3 Probability and extent of added benefit

The company presented no data for the assessment of the added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT as first-line treatment in adult patients with metastatic NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression ≥ 50%. An added benefit of ipilimumab + nivolumab + platinum-based chemotherapy is therefore not proven for research question 1.

This concurs with the company's assessment.

2.4 Research question 2: PD-L1 expression < 50%

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ipilimumab + nivolumab (status: 5 October 2020)
- bibliographical literature search on ipilimumab + nivolumab (last search on 1 October 2020)
- search in trial registries/trial results databases for studies on ipilimumab + nivolumab (last search on 5 October 2020)
- search on the G-BA website for ipilimumab + nivolumab (last search on 5 October 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ipilimumab + nivolumab (last search on 15 December 2020)

The check did not identify any additional relevant studies.

2.4.1.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[c] (yes/no [citation])	Publication (yes/no [citation])
CA209-9LA	Yes	Yes	No	No[d]	Yes [4-6]	Yes [7]

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. Study for which the company was sponsor.
c. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

The CA209-9LA study was used for the benefit assessment. The study pool concurs with that of the company.

The specification of the research question (patients with PD-L1 expression < 50%) and of the ACT (choice of the platinum component) resulted in restrictions that only apply to a subpopulation of the CA209-9LA study. This is explained in more detail in the following Section 2.4.1.2.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the included study – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
CA209-9LA	RCT, open-label, parallel	Adults (≥ 18 years) with histologically confirmed non-squamous or squamous stage IIIB[b] or IV NSCLC without EGFR mutation or ALK translocation and with an ECOG PS ≤ 1, without prior systemic therapy[d]	▪ Ipilimumab + nivolumab + platinum-based chemotherapy[a] (N = 361) ▪ platinum-based chemotherapy[a] (N = 358) Relevant subpopulation thereof[e]: ▪ ipilimumab + nivolumab + platinum-based chemotherapy[a] (n = 181) ▪ platinum-based chemotherapy[a] (n = 160)	Screening: ND Treatment: until disease progression, unacceptable toxicity, treatment discontinuation at the decision of the physician or patient, or reaching the maximum duration of therapy (24 months for ipilimumab + nivolumab) Observation[f]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	103 centres in Argentina, Australia, Belgium, Brazil, Canada, Chile, China, France, Germany, Ireland, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, United Kingdom, USA 8/2017–ongoing Data cut-offs: 3 October 2019[g] 9 March 2020[h]	Primary: overall survival Secondary: symptoms, health status, AEs

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. 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.
c. The G-BA assumes that patients in stage IIIB are not covered by the present therapeutic application. According to the company, 98% of the patients were in stage IV at the time of enrolment.
d. Related to NSCLC stage IIIB or IV, respectively.
e. The relevant subpopulation comprises patients with PD-L1 expression < 50% who were treated in accordance with the AM-RL criteria for the off-label use (Appendix VI to Section K [3]) of carboplatin. The relevant subpopulation corresponds to the subgroup of patients with non-squamous histology presented by the company (see Section 2.4.1.2).
f. Outcome-specific information is provided in Table 8.
g. Planned after the occurrence of 322 deaths.
h. Planned after the occurrence of 402 deaths.

Table 6: Characteristics of the included study – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
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: Federal Joint Committee; n: relevant subpopulation; N: number of randomized (included) patients; ND: no data; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus						

Table 7: Characteristics of the intervention – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Intervention	Comparison
CA209-9LA	Nivolumab 360 mg IV every 3 weeks, for a maximum of 24 months + ipilimumab 1 mg/kg BW IV every 6 weeks, for a maximum of 24 months + histology-based chemotherapy for a maximum of 2 cycles of 3 weeks each: ▪ squamous histology: carboplatin AUC 6 IV + paclitaxel 200 mg/m² BSA IV on day 1 of each cycle ▪ non-squamous histology[b]: cisplatin 75 mg/m² BSA IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle *or* carboplatin AUC 5–6 IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle	Histology-based chemotherapy for a maximum of 4 cycles of 3 weeks each: ▪ squamous histology: carboplatin AUC 6 IV + paclitaxel 200 mg/m² BSA IV on day 1 of each cycle ▪ non-squamous histology[b]: cisplatin 75 mg/m² BSA IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle *or* carboplatin AUC 5–6 IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle ▪ Patients with non-squamous histology and no disease progression could continue to receive maintenance therapy with pemetrexed 500 mg/m² BSA IV on day 1 of each cycle from cycle 5 onwards at the discretion of the investigator.
	▪ If nivolumab was discontinued, the therapy with ipilimumab also had to be stopped. If ipilimumab was discontinued, nivolumab could be continued. ▪ If ipilimumab or nivolumab was discontinued, therapy with chemotherapy[a] could be continued until 2 cycles were reached (and vice versa). ▪ Interval prolongations of the dose due to toxicity were possible. Dose adjustments were only allowed for chemotherapy[a]. ▪ Premedication for the administration of chemotherapy[a] was carried out in accordance with the SPC or local standards.	

Table 7: Characteristics of the intervention – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%) (multipage table)

Study	Intervention	Comparison
	Non-permitted pretreatment ▪ systemic antineoplastic therapy as primary therapy for stage IIIB or IV NSCLC ▪ systemic immunosuppressive therapies within 14 days before start of the study medication (with the exception of systemic glucocorticoids < 10 mg/day prednisone equivalent) **Permitted pretreatment** ▪ chemotherapy (adjuvant and neoadjuvant) and radiotherapy in early stage or locally advanced stage NSCLC up to ≥ 6 months before enrolment ▪ palliative radiotherapy of non-CNS metastases CNS up to ≥ 14 days before start of the study medication ▪ treatment of CNS metastases: either completion of glucocorticoid therapy or stable or reduced dose to ≤ 10 mg/day prednisone or equivalent ≥ 2 weeks before start of the study medication ▪ major surgery ≥ 14 days before start of the study medication **Concomitant treatment** ▪ inhaled, topical, ocular, intraarticular, and intranasal glucocorticoids ▪ adrenal replacement glucocorticoids > 10 mg prednisone equivalent ▪ < 3 weeks glucocorticoids for prophylaxis of allergic reactions or for treatment of non-autoimmune conditions ▪ bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events from bone metastases if therapy was initiated before start of the study medication ▪ palliative radiotherapy[c] and surgical resection of symptomatic bone, skin or CNS lesions ▪ palliative treatment of lesions causing haemoptysis	

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.
b. The choice of cisplatin or carboplatin was made by the investigator before randomization.
c. Ipilimumab and nivolumab had to be interrupted 1 week before, during and after radiotherapy.

AUC: area under the curve; BSA: body surface area; BW: body weight; CNS: central nervous system; IV: intravenous; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RANK-L: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial; vs.: versus

The CA209-9LA study is an ongoing, open-label, multicentre RCT comparing ipilimumab + nivolumab + platinum-based chemotherapy (hereinafter referred to as "intervention arm") with platinum-based chemotherapy (hereinafter referred to as "comparator arm").

The study included adult patients with squamous and non-squamous stage IV NSCLC without EGFR mutation or ALK translocation and ECOG PS ≤ 1 irrespective of the PD-L1 expression. The inclusion criteria of the CA209-9LA study additionally comprised patients with stage IIIB disease without the option of curative therapy. However, this only applied to 2% of the patients included. Patients with untreated brain metastases were excluded from the study. No prior systemic therapy of the stage IIIB or IV NSCLC was allowed.

The PD-L1 expression of the tumour tissue was determined using a DAKO immunohistochemistry kit by a central laboratory during the screening period, measuring the percentage of at least 100 viable tumour cells showing partial or complete membrane staining (= Tumour Proportion Score [TPS]). Unless stated otherwise, the PD-L1 expression stated in the present dossier assessment refers to the analyses based on TPS.

The tumour tissue from patients with non-squamous histology was tested locally for EGFR-mutations using a PCR-based assay. Tests approved by the Food and Drug Administration were to be used for this purpose. Patients with unknown EGFR status were excluded from the study. A test for ALK translocations was not mandatory, but patients with known ALK translocation were excluded from the study.

The CA209-9LA study included a total of 719 patients, randomized in a 1:1 ratio either to treatment with ipilimumab + nivolumab + platinum-based chemotherapy (N = 361) or to treatment with platinum-based chemotherapy alone (N = 358). The type of chemotherapy was dependent on the histology of the tumour: patients with squamous histology received carboplatin in combination with paclitaxel; patients with non-squamous histology received either cisplatin or carboplatin in combination with pemetrexed. The platinum component was chosen by the investigator before randomization on the basis of eligibility criteria not described in more detail by the company. Only the subpopulation of patients with non-squamous histology is relevant for the present research question (see below for explanations regarding the relevant subpopulation).

Randomization was stratified by PD-L1 expression (≥ 1% versus < 1%), histology of the tumour (squamous histology versus non-squamous histology) and sex (male versus female). Patients with non-quantifiable PD-L1 status (tumours with unmeasurable PD-L1 expression or insufficient sample quality for determination of PD-L1 expression) were assigned to the population with PD-L1 expression < 1% for stratification.

According to the company, besides this global study, there is an additional substudy in China for which no data were available at the time of submission of the dossier.

The therapy with ipilimumab as well as nivolumab complied with the requirements of the respective SPCs [8,9]. The maximum treatment duration for ipilimumab + nivolumab is 24 months. However, only < 5% of the patients have reached this treatment duration yet. In both treatment arms, the use of platinum-based chemotherapy for patients with non-squamous histology and PD-L1 expression < 50% also complied with the recommendations of the guideline and the requirements of the SPC [10-13] or the AM-RL for the off-label use of carboplatin in the therapeutic indication of NSCLC (Appendix VI to Section K of the AM-RL [3]) (see below). In the comparator arm, up to 4 cycles of chemotherapy were administered; then patients with non-squamous histology and no disease progression could receive maintenance therapy with pemetrexed from cycle 5. However, the number of patients who received maintenance therapy with pemetrexed cannot be inferred from Module 4 F.

Treatment was given until disease progression (determined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), unacceptable intolerance, withdrawal of consent, or reaching the maximum duration of therapy. Under certain conditions, therapy could be continued also beyond disease progression at the discretion of the investigator. An originally planned therapy with ipilimumab + nivolumab of up to 1 year after disease progression in addition to the maximum therapy duration was removed from the study protocol with Amendment 2 dated 2 July 2018. Switching patients from the comparator arm to treatment with ipilimumab + nivolumab after disease progression was not permitted. There were no restrictions regarding subsequent therapies.

Primary outcome of the CA209-9LA study was overall survival. Secondary patient-relevant outcomes were recorded in the categories of morbidity and side effects.

The patients underwent outcome-specific observation, at most until death, withdrawal of consent or end of the study. The study will be ended after the last visit or the last scheduled procedure of the last patient.

Relevant subpopulation of the CA209-9LA study

PD-L1 status

The company used a subpopulation of the CA209-9LA study to answer the present research question 2. These are patients with metastatic non-squamous or squamous NSCLC whose tumours have a PD-L1 expression < 50% (N = 497). Patients with non-quantifiable PD-L1 expression (tumours with unmeasurable PD-L1 expression or insufficient sample quality for determination of PD-L1 expression) were not included in the subpopulation. This applied to 21 patients in the intervention arm and to 25 patients in the comparator arm. The exclusion of these patients is appropriate.

Implementation of the Pharmaceutical Directive on the use of carboplatin

Carboplatin is only approved in combination with nab-paclitaxel [14] for the therapy of NSCLC in first-line treatment, but not in combination with other third-generation cytostatic agents. According to the current version of Appendix VI to Section K of the AM-RL [3], carboplatin can be prescribed in off-label use for patients with advanced NSCLC. Application in accordance with the directive is suitable for patients who are candidates for platinum-based combination therapy with a third-generation cytostatic agent such as paclitaxel, docetaxel or gemcitabine. In each case, the choice of the platinum component (carboplatin or cisplatin) should be based on the different toxicity profiles of the 2 substances and on the existing comorbidities [3].

In the CA209-9LA study, treatment with carboplatin was not explicitly restricted according to these criteria. The choice of chemotherapy was based on the histology of the tumour. All patients with squamous histology received therapy with carboplatin. A choice of the platinum component based on the different toxicity profiles and existing comorbidities was not planned. Thus, the criteria of the AM-RL were not implemented for patients with squamous histology. It is possible that the treatment with carboplatin for some of these patients was nevertheless

carried out according to the criteria of the AM-RL. However, the company did not differentiate the patients with squamous histology who were treated with carboplatin according to these criteria in Module 4 F. The treatment of patients with squamous histology therefore did not correspond to the ACT specified by the G-BA. The group of patients with squamous histology and PD-L1 expression < 50% is therefore not suitable for deriving an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy compared with the ACT.

For patients with non-squamous histology, the investigator could choose between treatment with carboplatin or cisplatin on a patient-specific basis before randomization. However, therapy with cisplatin was only possible if the patients fulfilled predefined eligibility criteria. The company did not present these eligibility criteria in Module 4 F. It thus remains unclear on what basis a decision was made as to whether a patient was suitable for therapy with cisplatin. Approximately 30% of the patients with non-squamous histology received therapy with cisplatin based on these eligibility criteria. It is possible that a larger proportion of these patients would have been suitable for therapy with cisplatin, especially since only patients in good general condition (ECOG-PS ≤ 1) were included in the CA209-9LA study.

German [12,15] and international guidelines [16,17] uniformly recommend selecting the platinum component in the therapeutic indication of NSCLC on a patient-specific basis, based on comorbidities, expected toxicity and general condition. This largely corresponds to the requirements of the AM-RL. Assuming that the eligibility criteria for therapy with cisplatin defined in the study protocol were based on the recommendations of these guidelines, the choice of the platinum component in the CA209-9LA study is considered to be a sufficient implementation of the AM-RL and thus the ACT for research question 2, despite the uncertainties described above.

Summary

The subpopulation of the CA209-9LA study presented by the company is not suitable for answering the research question of the present benefit assessment because the ACT specified by the G-BA was not implemented for patients with squamous NSCLC. The results of the subpopulation of patients with metastatic non-squamous NSCLC whose tumours have a PD-L1 expression < 50% were therefore used in the present benefit assessment. Analyses of this subpopulation relevant for the benefit assessment were available in Module 4 F in the form of subgroup analyses on histology.

Thus, no usable data were available for patients with squamous NSCLC.

Data cut-offs

The CA209-9LA study is still ongoing. So far, 2 data cut-offs are available:

- First data cut-off from 3 October 2019: interim analysis on overall survival, planned after 322 events

- Second data cut-off from 9 March 2020: final analysis on overall survival, planned after 402 events

A second interim analysis was removed from the study protocol by Amendment 4 dated 8 March 2019. The preplanned final analysis of the CA209-9LA study was used for the benefit assessment. This concurs with the company's approach.

Treatment duration and follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CA209-9LA	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up, or end of study
Morbidity	
Symptoms (LCSS ASBI)	35 and 115 days after the last study medication
Health status (EQ-5D VAS)	35 and 115 days after the last study medication, then every 3 months in the first year, then every 6 months
All outcomes in the category of side effects	100 days after the last study medication

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.

ASBI: average symptom burden index; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; VAS: visual analogue; vs.: versus

The observation periods for the outcomes on symptoms and side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 115 or 100 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival and health status.

Characteristics of the study population

Module 4 F contained no information on the patient characteristics for the relevant subpopulation. In the subpopulation presented by the company, the patient characteristics are balanced between the treatment arms.

Information on the course of the study

Data on the treatment duration or the observation period for individual outcomes are not available for the relevant subpopulation.

Module 4 F presented the treatment and observation periods for the subpopulation presented by the company, irrespective of histology. These are not suitable for estimating treatment and observation periods for the relevant subpopulation due to the different therapy structure based on histology in the comparator arm (fixed therapy duration for squamous histology versus optional maintenance therapy with pemetrexed for non-squamous histology). It is therefore unclear to what extent the treatment and observation periods differ between the treatment arms of the relevant subpopulation. See Section 2.4.2.2 for the effects on the outcome-specific risk of bias.

Information on subsequent therapies

There is no information on the administered subsequent therapies for the relevant subpopulation. Switching patients from the comparator arm to treatment with ipilimumab + nivolumab after disease progression was not permitted. There were no other specifications regarding subsequent therapies.

The data based on the subpopulation presented by the company show differences in the subsequent therapies between the intervention and the comparator arm. Fewer patients in the intervention arm (35.9%) received subsequent therapy than in the comparator arm (46.0%). A clear difference between the treatment arms was seen in the immunotherapies administered as subsequent therapy: Immunotherapies constituted about 14% of the administered follow-up therapies in the intervention arm and about 63% in the comparator arm. This is in line with the recommendations of the S3 guideline [12], which does not recommend further immunotherapy in the subsequent line after administration of immunotherapy, whereas immunotherapy should be administered in the subsequent line after administration of chemotherapy. Apart from that, the subsequent therapies in both treatment arms are largely comparable.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a] (research question 2: PD-L1 expression < 50%)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CA209-9LA	Yes	Yes	No	No	Yes	Yes	Low

a. Non-squamous histology: cisplatin or carboplatin in combination with pemetrexed; squamous histology: carboplatin in combination with paclitaxel.

PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the CA209-9LA study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.4.2.2.

Transferability of the study results to the German health care context

According to the company, the results of the CA209-9LA study can be transferred well to the German health care context, since the study was conducted in Germany and in Western industrialized countries with similar population groups (about 68% of the study population) and about 90% of the patients were of white family origin.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded with the LCSS ASBI
  - health status recorded with the EQ-5D VAS
- Side effects

- SAEs
- severe AEs, operationalized as CTCAE grade ≥ 3 events
- discontinuation due to AEs
- immune-related AEs (AEs, SAEs and severe AEs)
- further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 F).

Table 10 shows for which outcomes data for the relevant subpopulation with PD-L1 expression < 50% and non-squamous histology were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]; non-squamous histology (research question 2: PD-L1 expression < 50%)

Study	Outcomes								
	Overall survival	Symptoms (LCSS ASBI)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related AEs (AEs, SAEs and severe AEs)	Further specific AEs
CA209-9LA	Yes	No[c]	No[c]	No[d]	Yes	Yes	No[c]	No[c]	No[c]

a. Cisplatin or carboplatin in combination with pemetrexed.
b. Operationalized as CTCAE grade ≥ 3.
c. No usable data available; for reasons, see Section 2.4.2.1.
d. Outcome not recorded.

AE: adverse event; ASBI: average symptom burden index; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

- Outcomes on symptoms (LCSS ASBI) and health status (EQ-5D VAS): The company presented responder analyses for the outcomes on symptoms (LCSS ASBI) and health status (EQ-5D VAS) for the time to deterioration by 15 points and 7 mm, respectively. In Module 4 F, the company defined the deterioration that it described as definitive as follows: deterioration by at least the response threshold without subsequent improvement to a change from baseline < response threshold, or deterioration by at least the response

threshold and no subsequent values. It is not clear whether a subsequent improvement refers exclusively to the next subsequent recording or to all further subsequent recordings. Furthermore, it remains unclear in the formulation of the company how exactly the subsequent improvement is operationalized.

Notwithstanding the ambiguities mentioned, due to the operationalization, both a first deterioration and a deterioration persisting in 2 (or more) consecutive recordings can be rated as an event, depending on when the event occurred and how long the patients were observed afterwards. Such a comparison is not appropriate. It is unclear how many patients were included in the analysis as an event due to a first deterioration rather than a deterioration persisting over 2 or more consecutive recordings.

In addition, no questionnaire response rates, no information on treatment and observation periods and no Kaplan-Meier curves for the event time analyses are available for the relevant subpopulation. These are necessary to check whether an operationalization for permanent deterioration in the present data constellation – regardless of the fundamental problem of the operationalization mentioned above – could enable a fair comparison between the treatment arms at all.

Alternative types of analysis (e.g. responder analyses for the time to first deterioration or mixed-effects model with repeated measures [MMRM] analyses) are not available for the relevant subpopulation. Overall, no usable data are available for the outcomes on symptoms (LCSS ASBI) and health status (EQ-5D VAS).

It should additionally be noted that only analyses with a response criterion of 7 mm are available for the EQ-5D VAS. As explained in the General Methods of the Institute [1,18], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range).

- Discontinuation due to AEs: Only analyses for discontinuation of all drug components are available for the relevant subpopulation. Analyses for discontinuation of at least 1 drug component are missing. The operationalization “discontinuation of all drug components” is not usable for the benefit assessment in the present situation. 4 drugs were administered in the intervention arm and 2 drugs in the comparator arm. Patients in the intervention arm could partly continue treatment with the remaining drugs after discontinuation of individual drugs according to the study protocol (see Table 7). For patients in the comparator arm, it is not clear from the study protocol that both drug components had to be discontinued if the study medication was discontinued, but this can be assumed – also in view of the results of the subpopulation presented by the company, which show identical event rates for the comparator arm for both operationalizations. Thus, discontinuation due to AEs in the comparator arm, but not in the intervention arm, always corresponds to discontinuation of the entire treatment regimen, regardless of the operationalization. Therefore, an analysis of discontinuation of the entire treatment regimen alone cannot be meaningfully interpreted for the relevant subpopulation.

Regardless of this, discontinuation of at least one drug component is the preferable outcome, as any AE leading to discontinuation of any treatment component is relevant.

- Immune-related AEs: No usable data are available for immune-related AEs (AEs, SAEs and severe AEs). Although the company provided supplementary analyses for the AEs of special interest predefined in the study protocol (AESIs: specific immune-related AEs, specific AEs and other AEs of special interest), it is unclear whether these outcomes are suitable for an adequate representation of immune-related AEs in the CA209-9LA study. This is justified below.
  - It remains unclear whether the selection of the AESIs presented by the company was fundamentally based on the fact that their treatment required immunosuppression (e.g. with glucocorticoids). AEs that did not require systemic use of glucocorticoids would thus not be fully recorded.
  - Furthermore, the respective operationalizations of the individual AESIs are not clear from Module 4 F of the dossier. Thus, it remains unclear which events (e.g. Preferred Terms [PTs]) were included in the analyses.
  - Furthermore, there are no analyses of the AESIs for severe (e.g. operationalized as CTCAE grade ≥ 3) or serious events for the relevant subpopulation. Module 4 F only presented analyses of these outcomes for any AE.
- Further specific AEs: A choice of specific AEs is not possible because only incomplete data on common AEs, severe AEs (operationalized as CTCAE grade ≥ 3) and SAEs are available for the relevant subpopulation. Module 4 F only presented results for the relevant subpopulation for the common AEs/severe AEs/SAEs for which a statistically significant difference between the treatment groups was shown in the subpopulation presented by the company. In addition, due to the smaller number of patients, the absolute threshold values for the presentation of common AEs/severe AEs/SAEs are lower for the relevant subpopulation compared with the subpopulation presented by the company.

2.4.2.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]; non-squamous histology (research question 2: PD-L1 expression < 50%)

Study	Study level	Outcomes								
		Overall survival	Symptoms (LCSS ASBI)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Immune-related AEs (AEs, SAEs and severe AEs)	Further specific AEs
CA209-9LA	L	L	–[c]	–[c]	–[d]	H[e]	H[e]	–[c]	–[c]	–[c]

a. Cisplatin or carboplatin in combination with pemetrexed.
b. Operationalized as CTCAE grade ≥ 3.
c. No usable data available; for reasons, see Section 2.4.2.1.
d. Outcome not recorded.
e. Potential difference in observation periods between the treatment arms; potentially informative censorings.

AE: adverse event; ASBI: average symptom burden index; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; LCSS: Lung Cancer Symptom Scale; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the results of the outcome "overall survival" was rated as low. This concurs with the assessment of the company, which conducted the assessment for the subpopulation presented by it, however.

No usable data are available for the relevant subpopulation for the outcomes on symptoms, health status, discontinuation due to AEs, immune-related AEs, and further specific AEs. Health-related quality of life was not recorded in the CA209-9LA study. The risk of bias was therefore not assessed.

There is no information on treatment and observation period for the relevant subpopulation. It is therefore unclear whether there was a relevant difference in the treatment and observation periods between the treatment arms (see also Section 2.4.1.2). The risk of bias for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)" was therefore rated as high due to potentially different treatment and observation periods with potentially informative censoring. The company also assessed the risk of bias as high, but for the subpopulation presented by it and exclusively justified by the open-label study design.

2.4.2.3 Results

Table 12 summarizes the results of the comparison of ipilimumab + nivolumab + platinum-based chemotherapy versus platinum-based chemotherapy alone in patients with metastatic non-squamous NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50%. Where necessary, data from the company's dossier are supplemented by Institute's calculations.

Kaplan-Meier curves for the event-time analyses are not available for the relevant subpopulation, nor is a complete listing of frequent AEs, SAEs, severe AEs (operationalized as CTCAE grade ≥ 3) and discontinuation due to AEs, which is why these cannot be presented for the relevant subpopulation.

Table 12: Results (mortality, side effects) – RCT, direct comparison: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]; non-squamous histology (research question 2: PD-L1 expression < 50%)

Study Outcome category Outcome	Ipilimumab + nivolumab + platinum-based chemotherapy[a]		Platinum-based chemotherapy[a]		Ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[b]
CA209-9LA					
Mortality					
Overall survival	181	19.22 [14.23; NC] 88 (48.6)	160	11.33 [9.46; 13.86] 106 (66.3)	0.62 [0.47; 0.82]; < 0.001
Morbidity					
Symptoms (LCSS ASBI)		No usable data[c]			
Health status (EQ-5D VAS)		No usable data[c]			
Health-related quality of life	No outcomes recorded in this category				
Side effects					
AEs (supplementary information)[d]	180	0.16 [0.13; 0.23] 179 (99.4)	153	0.20 [0.13; 0.30] 150 (98.0)	–
SAEs[d]	180	5.29 [3.55; 8.84] 115 (63.9)	153	13.44 [7.10; NC] 67 (43.8)	1.59 [1.18; 2.15]; 0.002
Severe AEs[d, e]	180	3.02 [2.04; 3.98] 138 (76.7)	153	3.91 [2.79; 6.47] 99 (64.7)	1.27 [0.98; 1.64]; 0.071
Discontinuation due to AEs		No usable data[c]			
Immune-related AEs (AEs, SAEs and severe AEs)		No usable data[c]			
Further specific AEs		No usable data[c]			

a. Cisplatin or carboplatin in combination with pemetrexed.
b. Effect and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
c. No usable data available; for reasons, see Section 2.4.2.1.
d: Without recording of progression of the underlying disease.
e. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for the outcome "overall survival", and at most hints for the outcomes on SAEs and severe AEs (CTCAE grade ≥ 3) due to the high risk of bias.

Mortality

Overall survival

For the outcome "overall survival", there was a statistically significant effect in favour of ipilimumab + nivolumab + platinum-based chemotherapy for the relevant subpopulation. This resulted in an indication of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

This concurs with the company's assessment insofar as the company also derived an indication of an added benefit for overall survival. It conducted the assessment on the basis of the subpopulation formed by the company, however.

Morbidity

Symptoms (LCSS ASBI)

For the outcome "LCSS ASBI", no usable analyses were available for the relevant subpopulation (see Section 2.4.2.1). This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

This deviates from the assessment of the company, which, on the basis of the operationalization "definitive deterioration" and results of individual symptom scales of the LCSS, derived hints of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy for the outcome "LCSS" in the subpopulation formed by the company.

Health status (EQ-5D VAS)

For the outcome "EQ-5D VAS", no usable analyses were available for the relevant subpopulation (see Section 2.4.2.1). This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

This deviates from the assessment of the company, which, on the basis of the operationalization "definitive deterioration", derived hints of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy for the outcome "EQ-5D VAS" in the subpopulation formed by the company.

Health-related quality of life

The CA209-9LA study did not record health-related quality of life. This resulted in no hint of an added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; an added benefit is therefore not proven.

This deviates from the assessment of the company, which, on the basis of the LCSS, derived a hint of an added benefit for health-related quality of life in the subpopulation formed by the company.

Side effects

SAEs

For the outcome "SAEs", there was a statistically significant difference to the disadvantage of ipilimumab + nivolumab + platinum-based chemotherapy for the relevant subpopulation. This resulted in a hint of greater harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy.

This concurs with the assessment of the company insofar as it also derived a hint of greater harm from ipilimumab + nivolumab + platinum-based chemotherapy for the outcome "SAEs". It conducted the assessment on the basis of the subpopulation formed by the company, however.

Severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment groups for the outcome "severe AEs (CTCAE grade ≥ 3)" for the relevant subpopulation. This resulted in no hint of greater or lesser harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which, based on the subpopulation formed by the company, derived a hint of greater harm of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the outcome "severe AEs (CTCAE grade ≥ 3)".

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", no usable analyses were available for the relevant subpopulation (see Section 2.4.2.1). This resulted in no hint of greater or lesser harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company insofar, as it also derived no hint of greater or lesser harm of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the outcome "discontinuation due to AEs" (discontinuation of all drug components) based on the subpopulation formed by the company.

Specific AEs

Immune-related AEs (AEs, SAEs and severe AEs)

For the outcome "immune-related AEs (AEs, SAEs and severe AEs)", no usable analyses were available for the relevant subpopulation (see Section 2.4.2.1). This resulted in no hint of greater or lesser harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the company's approach insofar as the company did not use immune-related AEs for the assessment of the added benefit, but presented them only as supplementary information for the subpopulation formed by the company.

Further specific AEs

For further specific AEs, no usable analyses were available for the relevant subpopulation (see Section 2.4.2.1). This resulted in no hint of greater or lesser harm from ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy; greater or lesser harm is therefore not proven.

This deviates from the company's approach insofar as the company did not use further specific AEs for the assessment of the added benefit, but presented them only as supplementary information.

2.4.2.4 Subgroups and other effect modifiers

The derivation of the added benefit for research question 2 was conducted on the basis of patients with non-squamous histology and PD-L1 expression < 50%. No subgroup analyses are available for this patient group.

2.4.3 Probability and extent of added benefit

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

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

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 13).

Table 13: Extent of added benefit at outcome level: ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]; non-squamous histology (research question 2: PD-L1 expression < 50%)

Outcome category **Outcome**	**Ipilimumab + nivolumab + platinum-based chemotherapy[a] vs. platinum-based chemotherapy[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	19.22 vs. 11.33 HR: 0.62 [0.47; 0.82] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Symptoms (LCSS ASBI)	No usable data available[d]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data available[d]	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	5.29 vs. 13.44 HR: 1.59 [1.18; 2.15] HR: 0.63 [0.47; 0.85][e] p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Severe AEs	3.02 vs. 3.91 HR: 1.27 [0.98; 1.64] p = 0.071	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data available[d]	Greater/lesser harm not proven
Immune-related AEs (AEs, SAEs and severe AEs)	No usable data available[d]	Greater/lesser harm not proven
Further specific AEs	No usable data available[d]	Greater/lesser harm not proven

a. Cisplatin or carboplatin in combination with pemetrexed.
b. Probability provided if a statistically significant and relevant effect is present.
c. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
d. For reasons, see Section 2.4.2.1.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; PD-L1: programmed cell death ligand 1; SAE: serious adverse event; VAS: visual analogue; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 14 summarizes the results considered in the overall conclusion on the extent of added benefit.

Patients with non-squamous histology

Table 14: Positive and negative effects from the assessment of ipilimumab + nivolumab + platinum-based chemotherapy[a] in comparison with platinum-based chemotherapy[a]; non-squamous histology (research question 2: PD-L1 expression < 50%)

Positive effects	Negative effects
Mortality ▪ Overall survival: indication of added benefit – extent: "major"	–
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "considerable"
No usable data are available for the following outcomes: symptoms (LCSS ASBI), health status (EQ-5D VAS), discontinuation due to AEs, immune-related AEs (AEs, SAEs and severe AEs) and further specific AEs (see Section 2.4.2.1). Data on health-related quality of life were not recorded.	
a. Cisplatin or carboplatin in combination with pemetrexed. AE: adverse event; ASBI: average symptom burden index; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue; vs.: versus	

The overall picture shows one positive and one negative effect of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with platinum-based chemotherapy for the relevant subpopulation. On the side of positive effects, there is an indication of a major added benefit for the outcome "overall survival". On the side of negative effects, on the other hand, there is a hint of greater harm with the extent "considerable" for the outcome "SAEs". Overall, the negative effect in SAEs does not call into question the positive effect in overall survival. However, as no usable data are available for symptom outcomes (LCSS), health status (EQ-5D VAS), discontinuation due to AEs, immune-related AEs and further specific AEs, the overall extent of the added benefit is non-quantifiable.

In summary, there is an indication of a non-quantifiable added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT for patients with metastatic non-squamous NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50% in first-line treatment.

Patients with squamous histology

No relevant data are available for patients with metastatic squamous NSCLC without sensitizing EGFR mutation or ALK translocation and PD-L1 expression < 50% in first-line treatment. The added benefit is not proven for this patient group.

This deviates from the assessment of the company, which derived an indication of a major added benefit for all patients with PD-L1 expression < 50% regardless of histology.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ipilimumab + nivolumab + platinum-based chemotherapy in comparison with the ACT is summarized in Table 15.

Table 15: Ipilimumab in combination with nivolumab and 2 cycles of platinum-based chemotherapy – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) ≥ 50%[b]	Pembrolizumab as monotherapy	Added benefit not proven
2	First-line treatment of metastatic NSCLC without sensitizing EGFR mutation or ALK translocation in adults with PD-L1 expression (TPS) < 50%[b]	▪ **Cisplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]) *or* ▪ **carboplatin in combination with a third-generation cytostatic agent** (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed [except in mainly squamous histology]); see Appendix VI to Section K of the Pharmaceutical Directive *or* ▪ carboplatin in combination with nab-paclitaxel *or* ▪ pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology) *or* ▪ pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)	▪ Non-squamous histology: ▫ indication of an added benefit; extent "non-quantifiable"[c] ▪ Squamous histology: ▫ added benefit not proven

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. For the present therapeutic indication, it is assumed that patients have no medical indication for definitive local therapy.
c. Only patients with an ECOG PS of 0 or 1 were included in the CA209-9LA study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; TPS: Tumour Proportion Score

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

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a20-116.html.