IQWiG Reports – Commission No. A21-89

Nivolumab (malignant pleural mesothelioma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Nivolumab (malignes Pleuramesotheliom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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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
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D	European Quality of Life – 5 Dimensions
EMA	European Medicines Agency
EPAR	European Public Assessment Report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCSS-Meso	Lung Cancer Symptom Scale-Mesothelioma
mRECIST	modified Response Evaluation Criteria in Solid Tumours
PD-L1	programmed cell death ligand 1
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
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 nivolumab. 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 1 July 2021.

Research question

The aim of the present report is the assessment of the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in comparison with the appropriate comparator therapy (ACT) as first-line treatment of adults with unresectable malignant pleural mesothelioma.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of nivolumab + ipilimumab

Therapeutic indication	**ACT**[a]
First-line treatment of unresectable malignant pleural mesothelioma in adults	Treatment of physician's choice[b]

a. Presented is the ACT specified by the G-BA.
b. Guidelines recommend the use of pemetrexed + cisplatin, pemetrexed + carboplatin or bevacizumab + cisplatin + pemetrexed. The drugs bevacizumab and carboplatin are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In a clinical trial, the combination therapies of pemetrexed + cisplatin, pemetrexed + carboplatin and bevacizumab + cisplatin + pemetrexed are deemed suitable comparators.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's 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. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Study pool and study design

The study pool of the benefit assessment of nivolumab + ipilimumab in comparison with the ACT consists of the RCT CA209-743. This study compared nivolumab + ipilimumab with pemetrexed + cisplatin or pemetrexed + carboplatin. Therefore, this study is only suitable for drawing conclusions on the added benefit of nivolumab + ipilimumab for the patient group for which pemetrexed + cisplatin or pemetrexed + carboplatin represents a suitable treatment of

physician's choice. No data are available for patients for whom the treatment option of bevacizumab + cisplatin + pemetrexed is the suitable treatment of physician's choice.

Study CA209-743

Study CA209-743 is an ongoing, open-label, multicentre RCT on the comparison of nivolumab + ipilimumab with pemetrexed + cisplatin or pemetrexed + carboplatin.

The study included adult patients with untreated unresectable malignant pleural mesothelioma and measurable disease. Histological determination of the patient's tumour tissue (epithelioid versus non-epithelioid tumour histology) was required for study inclusion. Patients with undetermined tumour histology were excluded from study participation.

Study CA209-743 included a total of 605 patients, randomized in a 1:1 ratio either to treatment with nivolumab + ipilimumab (N = 303) or to pemetrexed + cisplatin or pemetrexed + carboplatin (N = 302).

In the intervention arm, treatment with nivolumab was conducted following a weight-based dosing regimen (3 mg/kg body weight every 2 weeks). The therapy with ipilimumab was in compliance with the requirements of the Summary of Product Characteristics (SPC). The maximum treatment duration with nivolumab + ipilimumab in the CA209-743 study was 24 months, which is in compliance with the requirements of the SPC of nivolumab.

The use of chemotherapy with pemetrexed + cisplatin or pemetrexed + carboplatin in the comparator arm was basically in compliance with the requirements of the SPC or with the guideline recommendations. Up to 6 cycles of chemotherapy were administered in the comparator arm.

Primary outcome of the CA209-743 study was overall survival. Secondary patient-relevant outcomes were recorded in the categories of morbidity and side effects.

Implementation of the appropriate comparator therapy in the CA209-743 study

The G-BA specified a treatment of physician's choice as the ACT, and, in its notes, listed pemetrexed + cisplatin, pemetrexed + carboplatin and bevacizumab + cisplatin + pemetrexed as treatment options. In the CA209-743 study presented by the company, pemetrexed + cisplatin or pemetrexed + carboplatin were used in the comparator arm; there was no comparison against the treatment option of bevacizumab + cisplatin + pemetrexed.

Overall, the treatment options of pemetrexed + cisplatin and pemetrexed + carboplatin used in the CA209-743 study represent relevant comparator therapies.

The CA209-743 study allows drawing conclusions on the added benefit of nivolumab + ipilimumab only for patients for whom pemetrexed + cisplatin or pemetrexed + carboplatin represents a suitable treatment option upon the physician's discretion.

Risk of bias

The risk of bias across outcomes for the CA209-743 study is rated as low. The outcome-specific risk of bias is rated as high for all patient-relevant outcomes except for overall survival.

Results

Hereinafter, the term "pemetrexed + platinum component" is used for pemetrexed + cisplatin or pemetrexed + carboplatin.

Mortality

Overall survival

A statistically significant difference in favour of nivolumab + ipilimumab was shown for the outcome of overall survival. In addition, there was an effect modification by the characteristic of tumour histology in this outcome. This results in an indication of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with non-epithelioid tumour histology. For patients with epithelioid tumour histology, this results in no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for this outcome; an added benefit is therefore not proven for these patients.

Morbidity

Health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])

The time to definitive deterioration by ≥ 15 points (scale range from 0 to 100) was considered for the outcome of EQ-5D VAS. There was a statistically significant difference in favour of nivolumab + ipilimumab in comparison with platinum-based chemotherapy. This results in a hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

Health-related quality of life

The CA209-743 study did not record health-related quality of life. This results in no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component; an added benefit is therefore not proven.

Side effects

Due to the substantially shorter planned treatment duration and the follow-up observation linked to the treatment duration, events in the comparator arm were taken into account only until approximately 8 months after randomization. A comparison of the 2 treatment arms is thus only possible for this period of the first 8 months after randomization, because all times of the patients still at risk in the comparator arm were censored after this period. Events in the comparator arm after this time point were thus not included in the estimation of the hazard ratio (HR).

Serious adverse events (SAEs)

A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown for the outcome of SAEs.

In addition, there was an effect modification by the characteristic of tumour histology in this outcome. For the outcome of SAEs, this results in a hint of greater harm of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with epithelioid tumour histology. For patients with non-epithelioid tumour histology, there is no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven for patients with non-epithelioid tumour histology.

Severe adverse events (AEs; Common Terminology Criteria for Adverse Events; [CTCAE] grade ≥ 3), discontinuation due to AEs (discontinuation of at least one drug component)

No statistically significant difference between the treatment groups was shown for the outcomes of severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs (discontinuation of at least one drug component). This results in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven.

Specific AEs

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

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with pemetrexed + platinum component was shown for the outcomes of immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3). This results in a hint of greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

Nausea (Preferred Term [PT], AEs), asthenia (PT, severe AEs), anaemia (PT, severe AEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs)

Statistically significant differences in favour of nivolumab + ipilimumab in comparison with pemetrexed + platinum component were shown for each of the following outcomes: nausea (PT, AEs), asthenia (PT, severe AEs), anaemia (PT, severe AEs), neutropenia (PT, severe AEs), and thrombocytopenia (PT, severe AEs). In each case, this results in a hint of lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

Diarrhoea (PT, AEs), renal and urinary disorders (System Organ Class [SOC], SAEs), endocrine disorders (SOC, SAEs), lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), musculoskeletal and connective tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with pemetrexed + platinum component was shown for each of the following outcomes: diarrhoea (PT, AEs), endocrine disorders (SOC, SAEs), lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), and musculoskeletal and connective tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]). In each case, this results in a hint of greater harm of nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with pemetrexed + platinum component was also shown for the outcome of renal and urinary disorders (SOC, SAEs). In addition, there was an effect modification by the characteristic of tumour histology in this outcome. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with epithelioid tumour histology. For patients with non-epithelioid tumour histology, there is no hint of lesser or greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven for patients with non-epithelioid tumour histology.

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

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

Data are available only for patients for whom pemetrexed + cisplatin or pemetrexed + carboplatin is a suitable treatment option concurring with treatment of physician's choice. No data are available for patients for whom the treatment option of bevacizumab + cisplatin + pemetrexed is the suitable treatment of physician's choice. The added benefit of nivolumab + ipilimumab is not proven for these patients.

[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].

Overall, there are both positive and negative effects of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients for whom pemetrexed + cisplatin or pemetrexed + carboplatin is a suitable treatment option concurring with treatment of physician's choice; some of them only for subgroups.

The positive effect in overall survival was only shown in patients with non-epithelioid tumour histology. For this reason, positive and negative effects are weighed separately for patients with epithelioid versus non-epithelioid tumour histology in the following text.

Patients with non-epithelioid tumour histology

On the side of positive effects, there is an indication of major added benefit in the outcome of overall survival for patients with non-epithelioid tumour histology. There is an additional hint of a minor added benefit for the outcome of health status. On the positive side, there are also hints of lesser harm with the extent "considerable" or "major" for individual specific severe AEs in the category of serious/severe side effects.

The positive effects are accompanied by negative effects in serious/severe side effects. There are hints of greater harm, some with the extent "major", for immune-related SAEs and immune-related severe AEs as well as individual specific SAEs/severe AEs.

No data are available for health-related quality of life.

Overall, the negative effects do not completely outweigh the advantage in overall survival, but result in a downgrading of the extent of added benefit. For patients with non-epithelioid tumour histology, there is therefore an indication of considerable added benefit.

Patients with epithelioid tumour histology

On the positive side, there is a hint of a minor added benefit for the outcome of health status for patients with epithelioid tumour histology. There are also hints of lesser harm with the extent "considerable" or "major" for individual specific severe AEs in the category of serious/severe side effects.

The positive effects are accompanied by negative effects in serious/severe side effects. There are hints of greater harm, some with the extent "major", for SAEs, immune-related SAEs and immune-related severe AEs as well as individual specific SAEs/severe AEs.

No data are available for health-related quality of life.

In summary, for patients with epithelioid tumour histology, there is no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component; an added benefit is therefore not proven.

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

Table 3: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of unresectable malignant pleural mesothelioma in adults	Treatment of physician's choice[b]	▪ Patients with epithelioid tumour histology[c]: added benefit not proven[d] ▪ Patients with non-epithelioid tumour histology[c]: indication of considerable added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. Guidelines recommend the use of pemetrexed + cisplatin, pemetrexed + carboplatin or bevacizumab + cisplatin + pemetrexed. The drugs bevacizumab and carboplatin are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In a clinical trial, the combination therapies of pemetrexed + cisplatin, pemetrexed + carboplatin and bevacizumab + cisplatin + pemetrexed are deemed suitable comparators.
c. For which pemetrexed + cisplatin or pemetrexed + carboplatin represents the suitable treatment of physician's choice.
d. Except for one patient, only patients with an ECOG PS of 0 or 1 were included in the CA209-743 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

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 nivolumab in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in comparison with the ACT as first-line treatment of adults with unresectable malignant pleural mesothelioma.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of nivolumab + ipilimumab

Therapeutic indication	**ACT**[a]
First-line treatment of unresectable malignant pleural mesothelioma in adults	Treatment of physician's choice[b]
a. Presented is the ACT specified by the G-BA. b. Guidelines recommend the use of pemetrexed + cisplatin, pemetrexed + carboplatin or bevacizumab + cisplatin + pemetrexed. The drugs bevacizumab and carboplatin are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In a clinical trial, the combination therapies of pemetrexed + cisplatin, pemetrexed + carboplatin and bevacizumab + cisplatin + pemetrexed are deemed suitable comparators. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's 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. RCTs were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on nivolumab + ipilimumab (status: 15 April 2021)
- bibliographical literature search on nivolumab + ipilimumab (last search on 21 April 2021)
- search in trial registries/trial results databases for studies on nivolumab + ipilimumab (last search on 22 April 2021)
- search on the G-BA website for nivolumab + ipilimumab (last search on 14 May 2021)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab + ipilimumab (last search on 8 July 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

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 and other sources[d] (yes/no [citation])
CA209-743	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7,8]

a. Cisplatin or carboplatin.
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.
c. Other sources: documents from the search on the G-BA website; European Public Assessment Report.
CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The CA209-743 study was used for the benefit assessment. The study pool concurs with that of the company.

The CA209-743 study compared nivolumab + ipilimumab with pemetrexed + cisplatin or pemetrexed + carboplatin. Therefore, this study is only suitable for drawing conclusions on the added benefit of nivolumab + ipilimumab for the patient group for which pemetrexed + cisplatin or pemetrexed + carboplatin represents a suitable treatment of physician's choice. No data are available for patients for whom the treatment option of bevacizumab + cisplatin + pemetrexed is the suitable treatment of physician's choice.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[b]
CA209-743	RCT, open-label, parallel	Adults (≥ 18 years) with histologically confirmed, untreated, unresectable malignant pleural mesothelioma and measurable disease[c] and an ECOG PS of 0 or 1	▪ Nivolumab + ipilimumab (N = 303) ▪ Pemetrexed + cisplatin or pemetrexed + carboplatin (N = 302)	Screening: 28 days Treatment: until disease progression[d], unacceptable toxicity, treatment discontinuation following the investigator's or patient's decision, or reaching the maximum duration of therapy (24 months for nivolumab + ipilimumab; 6 21-day cycles for pemetrexed + cisplatin or pemetrexed + carboplatin) Observation[e]: outcome-specific, at most until death, withdrawal of consent, or end of study	103 centres in Australia, Belgium, Brazil, Chile, China, Colombia, France, Germany, Greece, Italy, Japan, Mexico, Netherlands, Poland, Romania, Russia, South Africa, Switzerland, Turkey, United Kingdom, USA 11/2016–ongoing[f] Data cut-off: 3 April 2020[g]	Primary: overall survival Secondary: health status, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

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

a. Cisplatin or carboplatin.
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. Advanced unresectable disease that is not amenable to therapy with curative intent (surgery with or without chemotherapy); patients who had refused surgery were ineligible; measurable disease is defined as i) mesothelioma tumour thickness perpendicular to the chest wall or mediastinum, that can be measured in ≤ 2 positions at 3 separate levels on transverse cuts of CT scan (cuts must be ≥ 10 mm apart), for a total of ≤ 6 measurements (of ≥ 10 mm each), ii) non-pleural metastatic target lesions measured uni-dimensionally as per RECIST 1.1 criteria, iii) inclusion of patients without pleural lesions that can be considered measurable, but with metastatic lesions meeting criteria for target lesion by RECIST 1.1 criteria possible after consultation with the Medical Monitor.
d. Patients in the intervention arm could continue treatment with the study medication beyond initial progression (as defined by adapted mRECIST and/or RECIST 1.1 criteria) if the patient had a stable ECOG PS, an investigator-assessed clinical benefit and was tolerating the treatment. After further disease progression, treatment was to be discontinued.
e. Outcome-specific information is described in Table 8.
f. Follow-up observation of the patients still in the study is ongoing.
g. Planned interim analysis for the outcome of overall survival after the occurrence of 403 deaths; planned final analysis for the outcome of overall survival after at least 473 deaths; at the time of database closure (3 April 2020), 419 deaths had occurred, 5 patients in the intervention arm were still receiving treatment with the study medication at this time; due to superiority, the result of the interim analysis was considered the final result of the primary outcome of overall survival.

AE: adverse event; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; mRECIST: modified Response Evaluation Criteria in Solid Tumours; N: number of randomized patients; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study	Intervention	Comparison
CA209-743	Nivolumab 3 mg/kg BW IV every 2 weeks, for a maximum of 24 months + ipilimumab 1 mg/kg BW IV every 6 weeks, for a maximum of 24 months	Pemetrexed + platinum component[b] for a maximum of 6 cycles of 3 weeks each: ▪ cisplatin 75 mg/m² BSA IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle *or* ▪ carboplatin AUC 5 mg/mL/min IV + pemetrexed 500 mg/m² BSA IV on day 1 of each cycle
	▪ No dose adjustments allowed	▪ Dose reduction due to toxicity: ▫ a maximum of 2 dose reductions per study drug according to the protocol; continuation of the reduced dose for subsequent cycles
	▪ Dose delay due to toxicity: ▫ nivolumab: up to ≤ 6 weeks permitted ▫ ipilimumab: up to ≤ 12 weeks permitted ▫ in any case, a dose delay apples to both study drugs	▪ Dose delay due to toxicity: ▫ permitted for any study drug up to ≤ 6 weeks ▫ treatment with the other study medication may be continued at the discretion of the investigator
	▪ Treatment discontinuation due to toxicity: ▫ if nivolumab is discontinued, ipilimumab is also discontinued ▫ if ipilimumab is discontinued, nivolumab may be continued	▪ Treatment discontinuation due to toxicity: ▫ if cisplatin or carboplatin is discontinued: patients may continue treatment with pemetrexed and change the platinum component at the discretion of the investigator[c]
	Dose delay in case of investigator-assessed progression until confirmation of progression by the BICR; without confirmation of progression, treatment is continued	
	Premedication for the administration of chemotherapy[a] in accordance with the SPC or local requirements[d]	

Table 7: Characteristics of the intervention – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study	Intervention	Comparison
	Permitted pretreatment ▪ palliative radiotherapy < 2 weeks prior to first treatment and prophylactic radiotherapy to a pleurodesis drainage tract or biopsy site ▪ brain metastases that are surgically resected or treated with stereotaxic radiotherapy with no evolution and asymptomatic within ≤ 3 months before randomization, and on a stable or decreasing dose of ≤ 10 mg daily prednisone or equivalent for ≥ 2 weeks prior to first treatment **Non-permitted pretreatment** ▪ antibody therapy (e.g. anti-PD-L1, anti-PD-L2, anti-CTLA-4) ▪ chemotherapy (adjuvant, neoadjuvant), radical pleuropneumonectomy with or without intensity modulated radiotherapy, non-palliative radiotherapy ▪ intraoperative or intracavitary chemotherapy ▪ systemic treatment with either glucocorticoids (> 10 mg/day prednisone equivalent) or other immunosuppressants within ≤ 14 days prior to first treatment **Permitted concomitant treatment** ▪ topical, ocular, intra-articular, intranasal, and inhaled glucocorticoids ▪ adrenal replacement glucocorticoids > 10 mg/day prednisone equivalent ▪ < 3 weeks glucocorticoids for prophylaxis of allergic reactions or for treatment of non-autoimmune conditions **Non-permitted concomitant treatment** ▪ immunosuppressants ▪ palliative radiotherapy[e] on target or non-target lesions ▪ antineoplastic treatment (e.g. chemotherapy, hormonal therapy, immunotherapy, extensive non-palliative radiotherapy, standard or investigational drugs for treatment of pleural mesothelioma) ▪ live vaccines during treatment and ≤ 100 days post last dose	

a. Cisplatin or carboplatin.
b. Administration of cisplatin was preferred. The use of carboplatin was at the investigator's discretion.
c. Switching from cisplatin to carboplatin or vice versa was allowed. The reason for the use of carboplatin or for a treatment switch had to be documented in the electronic case report form.
d. Vitamins B12 and B9 supplementation and dexamethasone premedication.
e. If palliative radiotherapy of tumour lesions was required, nivolumab and ipilimumab had to be discontinued during and 2 weeks after radiotherapy.

AUC: area under the curve; BICR: blinded independent central review, BSA: body surface area; BW: body weight; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; IV: intravenous; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; RCT: randomized controlled

Study CA209-743 is an ongoing, open-label, multicentre RCT on the comparison of nivolumab + ipilimumab with pemetrexed + cisplatin or pemetrexed + carboplatin.

The study included adult patients with untreated unresectable malignant pleural mesothelioma and measurable disease. In the study, measurable disease was defined as i) mesothelioma tumour thickness perpendicular to the chest wall or mediastinum, that can be measured in ≤ 2 positions at 3 separate levels on transverse cuts of computed tomography (CT) scan (cuts must be ≥ 10 mm apart), for a total of ≤ 6 measurements (of ≥ 10 mm each), or ii) non-pleural

metastatic target lesions measured uni-dimensionally as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria. Inclusion of patients without pleural lesions that can be considered measurable, but with metastatic lesions meeting criteria for target lesion by RECIST 1.1 criteria was possible after consultation with the Medical Monitor. The inclusion criteria also comprised patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

The archival and/or fresh tumour tissue of the patients was determined histologically in the respective study centres by means of immunohistochemistry (epithelioid versus non-epithelioid tumour histology). Patients with undetermined tumour histology were excluded from study participation. In addition, the determination of programmed cell death ligand 1 (PD-L1) expression of the tumour tissue was a prerequisite for study inclusion. Patients were included in the study regardless of PD-L1 expression, however. The tumour sample had be shipped to a central laboratory within 42 days before randomization. PD-L1 expression was determined using a DAKO immunohistochemistry kit.

Study CA209-743 included a total of 605 patients, randomized in a 1:1 ratio either to treatment with nivolumab + ipilimumab (N = 303) or to pemetrexed + cisplatin or pemetrexed + carboplatin (N = 302). Randomization was stratified by tumour histology (epithelioid versus non-epithelioid) and sex (female versus male).

In the intervention arm, treatment with nivolumab was conducted following a weight-based dosing regimen (3 mg/kg body weight every 2 weeks). The approval specifies administration in a fixed dosage (360 mg every 3 weeks) irrespective of body weight [9]. According to the European Public Assessment Report (EPAR) by the European Medicines Agency (EMA), based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between the dosing regimens [8]. For the comparison examined in the present benefit assessment, it is assumed that the deviation regarding dose and dosing interval of nivolumab had no relevant influence on the observed effects. Treatment with ipilimumab was in compliance with the requirements of the SPC [10]. If treatment with ipilimumab was discontinued due to toxicity, continuation of treatment with nivolumab was possible. Discontinuation of treatment with nivolumab, on the other hand, also required discontinuation of treatment with ipilimumab. The maximum treatment duration with nivolumab + ipilimumab in the CA209-743 study was 24 months. This is in compliance with the maximum treatment duration specified in the SPC of nivolumab [9].

The use of chemotherapy with pemetrexed + cisplatin or pemetrexed + carboplatin in the comparator arm was basically in compliance with the requirements of the SPC [11] or with the guideline recommendations [12,13]. Up to 6 cycles of chemotherapy were administered in the comparator arm.

In both study arms, treatment continued until disease progression (as determined using RECIST version 1.1 and/or modified [m]RECIST criteria), unacceptable toxicity, treatment

discontinuation, or reaching of the maximum treatment duration. In the intervention arm, it was possible to continue therapy beyond disease progression at the discretion of the investigator under certain conditions. Switching to the treatment of the other study arm was not planned.

Primary outcome of the CA209-743 study was overall survival. Secondary patient-relevant outcomes were recorded in the categories of morbidity and side effects.

For the CA209-743 study, results of the data cut-off from 3 April 2020 are available. According to the study protocol, an interim analysis for the outcome of overall survival was available after 403 deaths. The final analysis for the outcome of overall survival was planned after at least 473 deaths. At the time point of the present data cut-off, 419 deaths had occurred. Due to the superiority, the result of the interim analysis was considered the final result of the primary outcome of overall survival.

Implementation of the appropriate comparator therapy in the CA209-743 study

The G-BA specified a treatment of physician's choice as the ACT, and, in its notes, listed pemetrexed + cisplatin, pemetrexed + carboplatin and bevacizumab + cisplatin + pemetrexed as treatment options. In the CA209-743 study presented by the company, pemetrexed + cisplatin or pemetrexed + carboplatin were used in the comparator arm; there was no comparison against the treatment option of bevacizumab + cisplatin + pemetrexed.

Even though, of the 2 platinum components, only cisplatin in combination with pemetrexed is approved in the present therapeutic indication, the combination with carboplatin is also recommended for malignant pleural mesothelioma according to guidelines [12,14-16]. Administration of cisplatin was preferred in the CA209-743 study. The use of carboplatin was at the investigator's discretion. Switching from cisplatin to carboplatin or vice versa was allowed. The reason for the use of carboplatin or for a treatment switch had to be documented in the electronic case report form.

The company considered the use of pemetrexed + cisplatin and pemetrexed + carboplatin to be an adequate implementation of the ACT, as the G-BA had designated these as suitable comparators, and the established guidelines [12-14,16] recommended these therapy regimens. The company stated that, in addition, the efficacy of both platinum components was comparable, which had been shown in clinical studies [17-20] and in everyday health care [21,22], and the EMA had designated the comparator arm of the CA209-743 study as the standard therapy in the therapeutic indication in the approval process. In contrast, the evidence for a bevacizumab-based triple combination was still limited and, in addition – as the company stated with reference to guidelines [12,13,16] – the patients had to be eligible for therapy with bevacizumab.

The company's reasoning regarding the non-consideration of the bevacizumab combination therapy as comparator is not adequate. Both carboplatin and bevacizumab are not approved in the present therapeutic indication, yet both drugs are recommended in guidelines in the present

therapeutic indication [12-16]. The company's statement that patients must be eligible for therapy with bevacizumab is correct insofar as guidelines recommend the use of bevacizumab only for certain patients (for example, bevacizumab is not recommended for patients with uncontrolled hypertension, bleeding or clotting risk, and substantial cardiovascular morbidity [12,16]). However, this is not a sufficient argument for not considering bevacizumab combination therapy for all patients in the CA209-743 study.

Overall, the treatment options of pemetrexed + cisplatin and pemetrexed + carboplatin used in the CA209-743 study represent relevant comparator therapies.

The CA209-743 study allows drawing conclusions on the added benefit of nivolumab + ipilimumab only for patients for whom pemetrexed + cisplatin or pemetrexed + carboplatin represents a suitable treatment option upon the physician's discretion.

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: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CA209-743	
Mortality	
Overall survival	Until death, end of study or withdrawal of consent
Morbidity	
Symptoms (LCSS-Meso)[b]	In the intervention arm until study discontinuation In the comparator arm[c] until disease progression And for both study arms for 30 and 120 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until death, end of study or withdrawal of consent
Health-related quality of life	Outcome not recorded[d]
Side effects	
All outcomes in the category of side effects	100 days after the last dose of the study medication

a. Cisplatin or carboplatin.
b. Information from the study protocol.
c. According to the information from the study protocol, it can be assumed that the patient was observed further if no disease progression occurred up to the last dose of the study medication.
d. The company assigned individual items (symptom burden, activity impairment, general health-related quality of life) of the LCSS-Meso to health-related quality of life. Regardless of the check of instrument validity, these 3 items are not suitable to represent the complex construct of health-related quality of life.

EQ-5D: European Quality of Life-5 Dimensions; LCSS-Meso: Lung Cancer Symptom Scale-Mesothelioma; RCT: randomized controlled trial; VAS: visual analogue scale

As survival, the patients' health status (EQ-5D VAS) in the CA209-743 study was observed in the survival follow-up until death, end of study or withdrawal of consent.

In the first 12 weeks, there were deviations in the EQ-5D documentation times (intervention arm: every 2 weeks; comparator arm: every 3 weeks). In addition, in both study arms, the recording was conducted before the study medication was administered at the start of the nivolumab or pemetrexed + cisplatin/carboplatin cycles, so that, in the in the first 12 weeks of the intervention arm, there were 4 health status recordings in the middle of the cycle of ipilimumab, which was administered every 6 weeks (see Table 7). However, since the recording was conducted over a much longer period of time, it is assumed that the above-mentioned aspects do not have a relevant influence on the result for the entire study period.

After the first 12 weeks, the EQ-5D VAS was recorded in both study arms every 6 weeks for the first 12 months, and then every 12 weeks. In the intervention arm, observation of the patients was continued beyond disease progression until study discontinuation. In the comparator arm, patients entered the follow-up observation phase in case of disease progression (recording of the EQ-5D VAS: 30 and 120 days after the last dose of study medication and every 3 months in the first year of survival follow-up, then every 6 months). Disease progression occurring in the comparator arm led to different recording intervals between the study arms during the course of the study. This does not call into question the usability of the data on health status recorded using the EQ-5D VAS, but is taken into account in the risk bias (see Section 2.4.2).

Unlike for health status, there was no follow-up observation until death, end of study or withdrawal of consent for the outcome of symptoms (Lung Cancer Symptom Scale-Mesothelioma [LCSS-Meso]). Although both study arms had the same planned follow-up observation of 30 days and 120 days after the last dose of the study medication, the planned observation periods differed between the study arms. Observation of the patients in the comparator arm of the CA209-743 study was only until disease progression, whereas observation of the patients in the intervention arm was continued beyond disease progression. Such a recording planned differently for the intervention arm and the comparator arm is not adequate. Regardless of the check of instrument validity, the data collected using LCSS-Meso are therefore unusable for the benefit assessment.

The observation periods for the outcomes on side effects were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 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

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

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study Characteristic Category	**Nivolumab + ipilimumab N[b] = 303**	**Pemetrexed + platinum component[a] N[b] = 302**
CA209-743		
Age [years], mean (SD)	69 (9)	68 (10)
Sex [F/M], %	23/77	23/77
Family origin, n (%)		
White	266 (88)	250 (83)
Asian	26 (9)	39 (13)
Other	11 (4)	13 (4)
Region, n (%)		
North America	32 (11)	27 (9)
Europe	177 (58)	175 (58)
Asia	26 (9)	39 (13)
Rest of the world	68 (22)	61 (20)
Disease duration: time between first diagnosis and randomization [years], (n%)		
< 1	296 (98)	291 (96)
≥ 1	7 (2)	11 (4)
Disease stage, n (%)		
I	12 (4)	20 (7)
II	23 (8)	22 (7)
III	103 (34)	106 (35)
IV	160 (53)	149 (49)
Not reported	5 (2)	5 (2)
ECOG PS, n (%)		
0	114 (38)	128 (42)
1	189 (62)	173 (57)
2[c]	0 (0)	1 (< 1)
Tumour histology[d], n (%)		
Epithelioid	236 (78)	235 (78)
Non-epithelioid	67 (22)	67 (22)
PD-L1 status[e], n (%)		
Positive (≥ 1%)[f]	232 (80)	219 (74)
Negative (< 1%)[f]	57 (20)	78 (26)
Smoking status, n (%)		
Never	127 (42)	122 (40)
Former	155 (51)	163 (54)
Current	18 (6)	8 (3)
Unknown	3 (1)	9 (3)

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study Characteristic Category	Nivolumab + ipilimumab N[b] = 303	Pemetrexed + platinum component[a] N[b] = 302
Treatment discontinuation[g], n (%)	292 (97)[h]	108 (38)[h]
Study discontinuation[i], n (%)	39 (13)	19 (7)

a. Cisplatin or carboplatin.
b. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
c. Inclusion criterion of the study: ECOG PS 0–1.
d. Based on the stratum used for randomization (IVRS data).
e. Determined using the Dako PD-L1 IHC 28-8 pharmDx test.
f. In relation to patients with quantifiable PD-L1 status (intervention arm N = 289; comparator arm N = 297).
g. In relation to patients who received at least one dose of the study medication (intervention arm N = 300; comparator arm N = 284). The most common reasons for treatment discontinuation in both treatment arms were progression (intervention arm 60.7%; comparator arm 15.5%) and toxicity of the study medication (intervention arm 19.7%; comparator arm 8.5%).
h. Institute's calculation based on the patients no longer under the study medication except for those who were recorded as patients who discontinued treatment for the reason of "not reported" in the electronic case report form, but had achieved the maximum treatment duration (intervention arm: 2 years, comparator arm: 18 weeks). At the data cut-off on 3 April 2020, these were 3 patients in the intervention arm and 176 patients in the comparator arm.
i. In relation to patients who received at least one dose of the study medication (intervention arm N = 300; comparator arm N = 284). The most common reason for study discontinuation in both treatment arms was death (intervention arm 8.0%; comparator arm 3.5%). It is unclear why these data differ from the event rates for the outcome "overall survival".

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; IHC: immunohistochemistry; IVRS: interactive voice response system; M: male; n: number of patients in the category; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

The patient characteristics between both treatment arms of the CA209-743 study were balanced. The clear majority of patients were men, of white family origin and on average about 69 years old. The time between first diagnosis and randomization in almost all patients (97%) was < 1 year. Most patients had stage III or IV disease. The majority of the patients had epithelioid tumour histology (78%) and positive (≥ 1%) PD-L1 status (about 77%). Discontinuation of treatment was reported more frequently for patients in the intervention arm (97%) than in the comparator arm (38%). The most common reason for treatment discontinuation was disease progression (intervention arm 60.7%; comparator arm 15.5%).

Information on the course of the study

Table 10 shows the median and mean treatment durations of the patients and the median and mean observation periods for individual outcomes.

Table 10: Information on the course of the study – – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study **Duration of the study phase** **Outcome category**	**Nivolumab + ipilimumab** **N = 303**	**Pemetrexed + platinum component[a]** **N = 302**
CA209-743		
Treatment duration[b] [months]		
Median [Q1; Q3]	5.55 [2.04; 11.35]	3.48 [2.66; 3.70]
Mean (SD)	7.88 (ND)	3.04 (ND)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	17.35 [8.64; 25.43]	13.27 [6.54; 22.97]
Mean (SD)	17.36 (9.92)	14.66 (9.67)
Morbidity		
Health status (EQ-5D VAS)	ND	
Health-related quality of life	Outcome not recorded	
Side effects	ND	

a. Cisplatin or carboplatin.
b. In relation to patients who received at least one dose of the study medication (intervention arm N = 300; comparator arm N = 284).

EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min: minimum; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration in the intervention arm of the CA209-743 study was about 2 months longer than in the comparator arm. The average treatment duration in the intervention arm was more than twice as long as in the comparator arm. This is mainly due to the fact that in the intervention arm, treatment with nivolumab + ipilimumab was possible until occurrence of disease progression or unacceptable toxicity or reaching the maximum treatment duration (24 months), while in the comparator arm, all patients were treated with a maximum of 6 cycles of chemotherapy.

The median observation period for the outcome of overall survival was about 4 months longer in the intervention arm; no data are available on the median or mean observation period for the outcomes of the categories of morbidity and side effects. For AEs, follow-up observation was only until 100 days after the last dose of study medication (see Table 8).

Information on subsequent therapies

The available information on the subsequent therapies administered (see Table 22 in Appendix B of the full dossier assessment) shows that a comparable proportion of patients in both study arms received systemic subsequent therapy (intervention arm: 44%, comparator arm: 41%). After discontinuation of the study medication, 3% of patients in the intervention arm and 20% of patients in the comparator arm received immunotherapy, with nivolumab being the most

commonly used drug. Chemotherapy as a subsequent therapy, however, was administered to more patients in the intervention arm (43%) than in the comparator arm (31%). Here, the most commonly used drug was pemetrexed (intervention arm: 40%, comparator arm: 16%), along with carboplatin (intervention arm: 29%, comparator arm: 13%). Other drugs used in ≥ 3% of patients each included gemcitabine, cisplatin and vinorelbine. Only few patients (about 7% in both study arms) received targeted therapy (including bevacizumab) and other investigational drugs. For patients with unresectable malignant pleural mesothelioma in second-line or subsequent therapy, guidelines recommend inclusion in clinical studies [13,14] or the use of unapproved drugs such as nivolumab alone or in combination with ipilimumab (unless used as first-line treatment), pembrolizumab, vinorelbine or gemcitabine [12]. Overall, the subsequent therapies used in the CA209-743 study are in line with guideline recommendations.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
CA209-743	Yes	Yes	No	No	Yes	Yes	Low

a. Cisplatin or carboplatin.
RCT: randomized controlled trial

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

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

Transferability of the study results to the German health care context

In the opinion of the company, the results of the CA209-743 study are readily transferable to the German health care context. In this regard, the company stated in the dossier that the study was conducted in Germany and in western industrialized countries (Europe and North America) with similar population groups (about 68% of the total population), and that approximately 85% of the study participants 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 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - health status recorded with the EQ-5D VAS
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (operationalized as CTCAE grade ≥ 3)
  - 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 Module 4 N of the dossier.

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

Table 12: Matrix of outcomes – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study	Outcomes								
	Overall survival	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Immune-related SAEs	Immune-related severe AEs[b]	Further specific AEs[b, d]
CA209-743	Yes	Yes	No[e]	Yes	Yes	Yes	Yes[f]	Yes[f]	Yes

a. Cisplatin or carboplatin.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as discontinuation of at least one drug component.
d. The following events (MedDRA coding) are considered: diarrhoea (PT, AEs), nausea (PT, AEs), renal and urinary disorders (SOC, SAEs), endocrine disorders (SOC, SAEs), asthenia (PT, severe AEs), lipase increased (PT, severe AEs), anaemia (PT, severe AEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), hepatobiliary disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs).
e. Outcome not recorded.
f. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("select AEs") is used.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

- Outcome on health status (EQ-5D VAS): For the outcome on health status (EQ-5D VAS), the company presented responder analyses for the time to definitive deterioration by 15 points, 10 points, and 7 points. In Module 4 N, the company defined definitive deterioration as follows: deterioration by at least the response threshold without subsequent improvement to a value above the response threshold or deterioration by at least the response threshold and no subsequent values. The company's dossier states that the definition likewise applies to all subsequent follow-up surveys. The company's analyses show that for some patients, an initial deterioration without further surveys was included in the analyses as an event; however, this was observed approximately equally in the 2 treatment arms and applied to few events (≤ 6%). Therefore, the results for time to definitive deterioration were used in the benefit assessment.

  The EQ-5D VAS response criterion of 15 points (scale range 0 to 100), which was used in the analyses presented by the company, fulfils the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as defined by the *General Methods* of the Institute [1]. The further responder analyses on the EQ-5D

VAS with a response criterion of 7 and 10 points provided by the company are presented as supplementary information in Appendix C of the full dossier assessment.

- Discontinuation due to AEs: In line with the company, discontinuation of at least one drug component is used as outcome for the benefit assessment, as any AE leading to discontinuation of any treatment component is relevant.
- Immune-related AEs: In Appendix 4-G of the dossier, the company provided supplementary analyses on AEs of special interest predefined in the study protocol (specific immune-related AEs ["imAEs"], specific AEs ("select AEs") and further AEs of special interest ["AESIs"]). In addition, analyses of severe events (operationalized as CTCAE grade ≥ 3) and serious events are available for these outcomes. In the dossier, the company stated that the outcome of AEs of special interest, which it referred to as "select AEs", was a choice of SOCs and PTs that belonged to the typical immune-related AEs and for which treatment of the AEs with immunosuppression (e.g. with corticosteroids) could, but did not have to, be necessary. In addition, it presented the list of PTs that were included as events in the analysis of the "select AEs". This operationalization is considered a sufficient approximation for immune-related AEs. Both severe AEs (CTCAE grade ≥ 3) and SAEs were considered.

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a]

Study	Study level	Outcomes								
		Overall survival	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Immune-related SAEs[d]	Immune-related severe AEs[b, d]	Further specific AEs[b, e]
CA209-743	L	L	H[f]	–[g]	H[h]	H[h]	H[i]	H[h]	H[h]	H[h, j]

a. Cisplatin or carboplatin.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Operationalized as discontinuation of at least one drug component.
d. In each case, the operationalization of the company-specific MedDRA PT collection from the outcome of adverse events of special interest ("select AEs") is used.
e. The following events (MedDRA coding) are considered: diarrhoea (PT, AEs), nausea (PT, AEs), renal and urinary disorders (SOC, SAEs), endocrine disorders (SOC, SAEs), asthenia (PT, severe AEs), lipase increased (PT, severe AEs), anaemia (PT, severe AEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs), hepatobiliary disorders (SOC, severe AEs), nervous system disorders (SOC, severe AEs), skin and subcutaneous tissue disorders (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs).
f. Large proportion of patients not included in the analysis (> 10%), decrease in the return of questionnaires in the course of the study, and lack of blinding in subjective recording of outcomes.
g. Outcome not recorded.
h. Incomplete observations for potentially informative reasons.
i. Lack of blinding in subjective recording of outcomes.
j. Non-serious/non-severe AEs: lack of blinding in subjective recording of outcomes.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Concurring with the company, the risk of bias of the result for the outcome of overall survival is rated as low, and that of the results for the outcomes of SAEs, severe AEs (overall rates and specific AEs), as well as immune-related SAEs/severe AEs as high. For the mentioned outcomes of the category of side effects, there are incomplete observations for potentially informative reasons due to the follow-up observation linked to the treatment duration and a possible association between outcome and reason for treatment discontinuation. Furthermore, lack of blinding is an additional reason for the high risk of bias of the results in non-serious and non-severe specific AEs. The risk of bias of the result for the outcome of discontinuation due to AEs is high due to the lack of blinding in subjective recording of outcomes alone.

Concurring with the company, the risk of bias of the result for the outcome of health status (EQ-5D VAS) is rated as high. Firstly, a high percentage (> 10%) of patients was excluded

from the analysis because either no baseline value at study start or no further value over the course of the study was available for them. Secondly, for the patients included in the analysis, the return of questionnaires decreased over time and differed between treatment arms. Besides, as described in Section 2.3.2, there were different recording intervals between the study arms during the course of the study. Lack of blinding with subjective outcome recording is an additional reason for the high risk of bias.

2.4.3 Results

Table 14 summarizes the results for the comparison of nivolumab + ipilimumab in comparison with pemetrexed + cisplatin or pemetrexed + carboplatin (hereinafter referred to as "pemetrexed + platinum component") as first-line treatment in adult patients with unresectable malignant pleural mesothelioma. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Event time analyses for the outcome of EQ-5D VAS with the response criteria of 7 and 10 points are presented in Appendix C of the full dossier assessment.

The available Kaplan-Meier curves on the outcomes included in the benefit assessment are presented in Appendix D of the full dossier assessment. The company did not present any Kaplan-Meier curves on the event time analyses for the EQ-5D VAS with the response threshold of 15 points or for immune-related and further specific AEs. Tables on common AEs, SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuations due to AEs are presented in Appendix E of the full dossier assessment.

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study Outcome category Outcome	Nivolumab + ipilimumab		Pemetrexed + platinum component[a]		Nivolumab + ipilimumab vs. pemetrexed + platinum component[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]
CA209-743					
Mortality					
Overall survival	303	18.07 [16.82; 21.45] 200 (66.0)	302	14.09 [12.45; 16.23] 219 (72.5)	0.74 [0.61; 0.89]; 0.002
Morbidity					
Health status (EQ-5D VAS[c])	303	26.15 [22.64; NC] 81 (26.7)	302	16.69 [15.01; 21.75] 99 (32.8)	0.65 [0.49; 0.88]; 0.005
Health-related quality of life	No outcomes recorded in this category				
Side effects[d]					
AEs (supplementary information)[e]	*300*	*0.26 [0.20; 0.39]* *298 (99.3)*	*284*	*0.13 [0.10; 0.20]* *276 (97.2)*	–
SAEs[e]	300	9.33 [7.56; 12.52] 163 (54.3)	284	NA 77 (27.1)	1.74 [1.31; 2.32]; < 0.001
Severe AEs[e, f]	300	7.13 [5.26; 9.79] 178 (59.3)	284	6.77 [3.55; NC] 139 (48.9)	0.91 [0.72; 1.15]; 0.418
Discontinuation due to AEs[e, g]	300	22.11 [17.58; NC] 92 (30.7)	284	NA 58 (20.4)	0.99 [0.69; 1.41]; 0.935
Immune-related AEs (supplementary information)	*300*	*1.48 [1.22; 1.87]* *236 (78.7)*	*284*	*NA* *107 (37.7)*	–
Immune-related SAEs	300	NA 66 (22.0)	284	NA 7 (2.5)	7.54 [3.42; 16.61]; < 0.001
Immune-related severe AEs[f]	300	NA [21.68; NC] 74 (24.7)		NA 11 (3.9)	4.62 [2.40; 8.87]; < 0.001
Diarrhoea (PT, AEs)	300	21.49 [15.11; NC] 98 (32.7)	284	NA 34 (12.0)	2.22 [1.48; 3.33]; < 0.001
Nausea (PT, AEs)	300	NA 76 (25.3)	284	NA [4.53; NC] 124 (43.7)	0.37 [0.28; 0.51]; < 0.001
Renal and urinary disorders (SOC, SAEs)	300	NA 13 (4.3)	284	NA 3 (1.1)	3.68 [1.03; 13.19]; 0.032
Endocrine disorders (SOC, SAEs)	300	NA 10 (3.3)	284	NA 1 (0.4)	7.76 [0.97; 62.03]; 0.022

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study Outcome category Outcome	Nivolumab + ipilimumab		Pemetrexed + platinum component[a]		Nivolumab + ipilimumab vs. pemetrexed + platinum component[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]
Asthenia (PT, severe AEs[f])	300	NA 4 (1.3)	284	NA 13 (4.6)	0.23 [0.07; 0.77]; 0.010
Lipase increased (PT, severe AEs[f])	300	NA 17 (5.7)	284	NA 1 (0.4)	11.72 [1.52; 90.15]; 0.003
Anaemia (PT, severe AEs[f])	300	NA 10 (3.3)	284	NA 39 (13.7)	0.17 [0.08; 0.37]; < 0.001
Neutropenia (PT, severe AEs[f])	300	NA 4 (1.3)	284	NA 45 (15.8)	0.04 [0.01; 0.16]; < 0.001
Thrombocytopenia (PT, severe AEs[f])	300	NA 4 (1.3)	284	NA 11 (3.9)	0.17 [0.04; 0.78]; 0.010
Hepatobiliary disorders (SOC, severe AEs[f])	300	NA 20 (6.7)	284	NA 0 (0)	NC; < 0.001
Nervous system disorders (SOC, severe AEs[f])	300	NA 15 (5.0)	284	NA 3 (1.1)	3.57 [0.99; 12.79]; 0.037
Skin and subcutaneous tissue disorders (SOC, severe AEs[f])	300	NA 14 (4.7)	284	NA 1 (0.4)	8.67 [1.10; 68.44]; 0.014
Musculoskeletal and connective tissue disorders (SOC, severe AEs[f])	300	NA 13 (4.3)	284	NA 2 (0.7)	4.42 [0.96; 20.45]; 0.037

a. Cisplatin or carboplatin.
b. Stratified Cox model and stratified log-rank test; each stratified by sex and histology.
c. Time to definitive deterioration. A decrease by ≥ 15 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
d. When interpreting the results on side effects, it should be noted that the substantially shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm result in the hazard ratio reflecting only approximately the first 8 months after randomization.
e. Without recording of progression of the underlying disease.
f. Operationalized as CTCAE grade ≥ 3.
g. Operationalized as discontinuation of at least one drug component.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

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

Mortality

Overall survival

A statistically significant difference in favour of nivolumab + ipilimumab was shown for the outcome of overall survival. In addition, there was an effect modification by the characteristic of tumour histology in this outcome. This results in an indication of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with non-epithelioid tumour histology. For patients with epithelioid tumour histology, this results in no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for this outcome; an added benefit is therefore not proven for these patients.

This deviates from the assessment of the company, which also described the effect modification, but derived an indication of an added benefit for the outcome of overall survival on the basis of the total population, regardless of tumour histology.

Morbidity

Health status (EQ-5D VAS)

The time to definitive deterioration by ≥ 15 points (scale range from 0 to 100) was considered for the outcome of EQ-5D VAS. There was a statistically significant difference in favour of nivolumab + ipilimumab in comparison with platinum-based chemotherapy. This results in a hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

This concurs with the company's assessment insofar as the company also derived a hint of an added benefit for the outcome of health status (EQ-5D VAS). It conducted the assessment on the basis of the response threshold of 7 points, however.

Health-related quality of life

The CA209-743 study did not record health-related quality of life. This results in no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component; an added benefit is therefore not proven.

This deviates from the approach of the company, which derived a hint of an added benefit for health-related quality of life on the basis of individual items of the LCSS-Meso (symptom burden, activity impairment, general health-related quality of life) as well as the index value of the 3 items.

Side effects

Due to the substantially shorter planned treatment duration and the follow-up observation linked to the treatment duration (see Table 8), events in the comparator arm were taken into account only until approximately 8 months after randomization. A comparison of the 2 treatment arms is thus only possible for this period of the first 8 months after randomization, because all times of the patients still at risk in the comparator arm were censored after this period. Events in the comparator arm after this time point were thus not included in the estimation of the HR.

SAEs

A statistically significant difference to the disadvantage of nivolumab + ipilimumab was shown for the outcome of SAEs.

In addition, there was an effect modification by the characteristic of sex and the characteristic of tumour histology in this outcome. Since a consistent effect modification for the characteristic of tumour histology was shown across several outcomes, particularly in the outcome of overall survival, only this characteristic is used for the assessment. The characteristic of sex is not considered further (see Section 2.4.4).

For the outcome of SAEs, this results in a hint of greater harm of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with epithelioid tumour histology. For patients with non-epithelioid tumour histology, there is no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven for patients with non-epithelioid tumour histology.

This deviates from the assessment of the company, which also described the effect modification, but derived a hint of greater harm for the outcome of SAEs on the basis of the total population, regardless of tumour histology.

Severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs (discontinuation of at least one drug component)

No statistically significant difference between the treatment groups was shown for the outcomes of severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs (discontinuation of at least one drug component). This results in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

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

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with pemetrexed + platinum component was shown for the outcomes of immune-

related SAEs and immune-related severe AEs (CTCAE grade ≥ 3). This results in a hint of greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

This deviates from the approach of the company, which did not use immune-related AEs for the assessment of the added benefit, but presented them only as supplementary information.

Nausea (PT, AEs), asthenia (PT, severe AEs), anaemia (PT, severe AEs), neutropenia (PT, severe AEs), thrombocytopenia (PT, severe AEs)

Statistically significant differences in favour of nivolumab + ipilimumab in comparison with pemetrexed + platinum component were shown for each of the following outcomes: nausea (PT, AEs), asthenia (PT, severe AEs), anaemia (PT, severe AEs), neutropenia (PT, severe AEs), and thrombocytopenia (PT, severe AEs). In each case, this results in a hint of lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

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

Diarrhoea (PT, AEs), renal and urinary disorders (SOC, SAEs), endocrine disorders (SOC, SAEs), lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), musculoskeletal and connective tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with pemetrexed + platinum component was shown for each of the following outcomes: diarrhoea (PT, AEs), endocrine disorders (SOC, SAEs), lipase increased (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), nervous system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), and musculoskeletal and connective tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]). In each case, this results in a hint of greater harm of nivolumab + ipilimumab in comparison with pemetrexed + platinum component.

A statistically significant difference to the disadvantage of nivolumab + ipilimumab in comparison with pemetrexed + platinum component was also shown for the outcome of renal and urinary disorders (SOC, SAEs). In addition, there was an effect modification by the characteristic of tumour histology in this outcome. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with epithelioid tumour histology. For patients with non-epithelioid tumour histology, there is no hint of lesser or greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven for patients with non-epithelioid tumour histology.

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

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- sex (female versus male)
- age (< 65 years versus ≥ 65 to < 75 years versus ≥ 75 years)
- tumour histology (epithelioid versus non-epithelioid)
- PD-L1 status (positive versus negative versus not reported)

For the outcome of health status, recorded using the EQ-5D VAS, there are no interaction tests and subgroup analyses for the response threshold of 15 points.

Overall, Kaplan-Meier curves on subgroup analyses are missing.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one subgroup.

Presented are only the results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. The results are shown in Table 15.

Table 15: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study Outcome Characteristic Subgroup	Nivolumab + ipilimumab N	Nivolumab + ipilimumab Median time to event in months [95% CI] Patients with event n (%)	Pemetrexed + platinum component[a] N	Pemetrexed + platinum component[a] Median time to event in months [95% CI] Patients with event n (%)	Nivolumab + ipilimumab vs. pemetrexed + platinum component[a] HR [95% CI][b]	Nivolumab + ipilimumab vs. pemetrexed + platinum component[a] p-value[c]
CA209-743						
Overall survival						
Tumour histology						
Epithelioid	236	18.73 [17.05; 21.72] 157 (66.5)	235	16.23 [14.09; 19.15] 164 (69.8)	0.85 [0.68; 1.06]	0.151
Non-epithelioid	67	16.89 [11.83; 25.20] 43 (64.2)	67	8.80 [7.62; 11.76] 55 (82.1)	0.46 [0.31; 0.70]	< 0.001
Total					Interaction:	0.003[d]
SAEs[e, f]						
Sex						
Female	68	17.87 [14.42; NC] 26 (38.2)	63	NA 21 (33.3)	0.68 [0.36; 1.30]	0.242
Male	232	7.89 [4.60; 9.66] 137 (59.1)	221	NA 56 (25.3)	2.19 [1.58; 3.02]	< 0.001
Total					Interaction:	0.002[d]
Tumour histology						
Epithelioid	233	9.23 [6.37; 12.45] 131 (56.2)	219	NA 53 (24.2)	1.98 [1.42; 2.76]	< 0.001
Non-epithelioid	67	9.72 [4.37; NC] 32 (47.8)	65	NA [4.47; NC] 24 (36.9)	1.13 [0.65; 1.97]	0.665
Total					Interaction:	0.031[d]
Renal and urinary disorders (SOC, SAEs)[f]						
Tumour histology						
Epithelioid	233	NA 12 (5.2)	219	NA 1 (0.5)	10.03 [1.28; 78.39]	0.007
Non-epithelioid	67	NA 1 (1.5)	65	NA 2 (3.1)	0.50 [0.05; 5.55]	0.567
Total					Interaction:	0.049[d]

Table 15: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Study Outcome Characteristic Subgroup	Nivolumab + ipilimumab		Pemetrexed + platinum component[a]		Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]	
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][b]	p-value[c]

a. Cisplatin or carboplatin.
b. Unstratified Cox model.
c. Unstratified log-rank test.
d. From unstratified Cox model with treatment, subgroup characteristic and interaction term between treatment and subgroup characteristic.
e. Without recording of progression of the underlying disease.
f. When interpreting the results on side effects, it should be noted that the substantially shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm result in the hazard ratio reflecting only approximately the first 8 months after randomization.

AE: adverse event; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Mortality

Overall survival

There was an effect modification by the characteristic of tumour histology for the outcome of overall survival. For patients with non-epithelioid tumour histology, a statistically significant difference was found in favour of nivolumab + ipilimumab versus pemetrexed + platinum component. This results in an indication of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with non-epithelioid tumour histology.

For patients with epithelioid tumour histology, in contrast, there was no statistically significant difference between treatment groups. For patients with epithelioid tumour histology, this results in no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component; an added benefit is therefore not proven for patients with epithelioid tumour histology.

Side effects

SAEs

For the outcome of SAEs, there was an effect modification by the characteristic of sex and by the characteristic of tumour histology. Since a consistent effect modification for the characteristic of tumour histology was shown across several outcomes, particularly in the

outcome of overall survival, only this characteristic is used for the assessment. The characteristic of sex is not considered further.

For patients with epithelioid tumour histology, a statistically significant difference was found to the disadvantage of nivolumab + ipilimumab versus pemetrexed + platinum component. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with epithelioid tumour histology. For patients with non-epithelioid tumour histology, in contrast, there was no difference between treatment groups. For patients with non-epithelioid tumour histology, this results in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven for patients with non-epithelioid tumour histology.

Specific AEs

Renal and urinary disorders (SOC, SAEs)

There was an effect modification by the characteristic of tumour histology for the outcome of renal and urinary disorders (SOC, SAEs). For patients with epithelioid tumour histology, a statistically significant difference was found to the disadvantage of nivolumab + ipilimumab versus pemetrexed + platinum component. This results in a hint of greater harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients with epithelioid tumour histology. For patients with non-epithelioid tumour histology, in contrast, there was no difference between treatment groups. For patients with non-epithelioid tumour histology, this results in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with pemetrexed + platinum component; greater or lesser harm is therefore not proven for patients with non-epithelioid tumour histology.

2.5 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.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 16).

Determination of the outcome category for symptom outcomes

For the following outcome, it cannot be inferred from the arguments in the company's dossier whether it is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

The company classified the outcome of health status, determined with the EQ-5D VAS, as serious. It justified this by stating that the symptoms of loss of appetite (and subsequent weight loss), fatigue, cough and pain, which the company also classified as serious, characterize the patients' situation at baseline. Irrespective of the influence of these symptoms on the patient's health status, it is unclear whether the symptoms mentioned are to be classified as serious/severe per se. No further information is available regarding a threshold for estimating the severity level. Therefore, the outcome of health status is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 16: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival Tumour histology Epithelioid	18.73 vs. 16.23 HR: 0.85 [0.68; 1.06] p = 0.151	Lesser/added benefit not proven
Non-epithelioid	16.89 vs. 8.80 HR: 0.46 [0.31; 0.70] p < 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Health status (EQ-5D VAS; definitive deterioration of 15 points)	26.15 vs. 16.69 HR: 0.65 [0.49; 0.88] p = 0.005 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects[d]		
SAEs Tumour histology Epithelioid	9.23 vs. NA HR: 1.98 [1.42; 2.76] HR: 0.51 [0.36; 0.70][e] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Non-epithelioid	9.72 vs. NA HR: 1.13 [0.65; 1.97] p = 0.665	Greater/lesser harm not proven
Severe AEs	7.13 vs. 6.77 HR: 0.91 [0.72; 1.15] p = 0.418	Greater/lesser harm not proven
Discontinuation due to AEs (discontinuation of at least one drug component)	22.11 vs. NA HR: 0.99 [0.69; 1.41] p = 0.935	Greater/lesser harm not proven

Table 16: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Immune-related SAEs	NA vs. NA HR: 7.54 [3.42; 16.61] HR: 0.13 [0.06; 0.29][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Immune-related severe AEs	NA vs. NA HR: 4.62 [2.40; 8.87] HR: 0.22 [0.11; 0.42][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Diarrhoea (AEs)	21.49 vs. NA HR: 2.22 [1.48; 3.33] HR: 0.45 [0.30; 0.68][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Nausea (AEs)	NA vs. NA HR: 0.37 [0.28; 0.51] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Renal and urinary disorders (SAEs) Tumour histology		
Epithelioid	NA vs. NA HR: 10.03 [1.28; 78.39] HR: 0.10 [0.01; 0.78][e] p = 0.007 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Non-epithelioid	NA vs. NA HR: 0.50 [0.05; 5.55] p = 0.567	Greater/lesser harm not proven
Endocrine disorders (SAEs)	NA vs. NA HR: 7.76 [0.97; 62.03] HR: 0.13 [0.02; 1.03][e] p = 0.022 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "minor"[f]
Asthenia (severe AEs)	NA vs. NA HR: 0.23 [0.07; 0.77] p = 0.010 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"

Table 16: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
Lipase increased (severe AEs)	NA vs. NA HR: 11.72 [1.52; 90.15] HR: 0.09 [0.01; 0.66][e] p = 0.003 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Anaemia (severe AEs)	NA vs. NA HR: 0.17 [0.08; 0.37] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Neutropenia (severe AEs)	NA vs. NA HR: 0.04 [0.01; 0.16] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% lesser harm, extent: "major"
Thrombocytopenia (severe AEs)	NA vs. NA HR: 0.17 [0.04; 0.78] p = 0.010 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Hepatobiliary disorders (severe AEs)	NA vs. NA HR: NC p < 0.001 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"
Nervous system disorders (severe AEs)	NA vs. NA HR: 3.57 [0.99; 12.79] HR: 0.28 [0.08; 1.01][e] p = 0.037 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "minor"[f]
Skin and subcutaneous tissue disorders (severe AEs)	NA vs. NA HR: 8.67 [1.10; 68.44] HR: 0.12 [0.01; 0.91][e] p = 0.014 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Musculoskeletal and connective tissue disorders (severe AEs)	NA vs. NA HR: 4.42 [0.96; 20.45] HR: 0.23 [0.05; 1.04][e] p = 0.037 probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "minor"[f]

Table 16: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. pemetrexed + platinum component[a] (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Nivolumab + ipilimumab vs. pemetrexed + platinum component[a]** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[b]**	**Derivation of extent[c]**
a. Cisplatin or carboplatin. 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. When interpreting the results on side effects, it should be noted that the substantially shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm result in the hazard ratio reflecting only approximately the first 8 months after randomization. e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. f. The result of the statistical test is decisive for the derivation of the added benefit; the extent is rated as "minor". AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue		

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of nivolumab + ipilimumab in comparison with pemetrexed + platinum component[a] (multipage table)

Positive effects	**Negative effects**
Mortality ▪ Overall survival ▫ Non-epithelioid tumour histology indication of an added benefit – extent: "major"	–
Morbidity ▪ Health status: hint of an added benefit – extent: "minor"	–
Serious/severe side effects[b] ▪ Severe AEs ▫ Asthenia (severe AEs): hint of lesser harm – extent: "considerable" ▫ Anaemia (severe AEs): hint of lesser harm – extent: "major" ▫ Neutropenia (severe AEs): hint of lesser harm – extent: "major" ▫ Thrombocytopenia (severe AEs): hint of lesser harm – extent: "considerable"	Serious/severe side effects[b] ▪ SAEs - Epithelioid tumour histology hint of greater harm – extent: "major" ▫ Immune-related SAEs: hint of greater harm – extent: major ▫ Renal and urinary disorders (SAEs) - Epithelioid tumour histology hint of greater harm – extent: "considerable" ▫ Endocrine disorders (SAEs): hint of greater harm – extent: "minor" ▪ Severe AEs ▫ Immune-related severe AEs: hint of greater harm – extent: "major" ▫ Lipase increased (severe AEs): hint of greater harm – extent: "major" ▫ Hepatobiliary disorders (severe AEs): hint of greater harm – extent: "non-quantifiable" ▫ Nervous system disorders (severe AEs): hint of greater harm – extent: "minor" ▫ Skin and subcutaneous tissue disorders (severe AEs): hint of greater harm – extent: "minor" ▫ Musculoskeletal and connective tissue disorders (severe AEs): hint of greater harm – extent: "minor"
Non-serious/non-severe side effects ▪ Nausea (AEs): hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ Diarrhoea (AEs): hint of greater harm – extent: "considerable"
Data on health-related quality of life were not recorded.	
a. Cisplatin or carboplatin. b. When interpreting the results on side effects, it should be noted that the substantially shorter planned treatment duration and the associated discontinuation of follow-up in the comparator arm result in the hazard ratio reflecting only approximately the first 8 months after randomization. AE: adverse event; SAE: serious adverse event	

Data are available only for patients for whom pemetrexed + cisplatin or pemetrexed + carboplatin is a suitable treatment option concurring with treatment of physician's choice. No data are available for patients for whom the treatment option of bevacizumab + cisplatin +

pemetrexed is the suitable treatment of physician's choice. The added benefit of nivolumab + ipilimumab is not proven for these patients.

Overall, there are both positive and negative effects of nivolumab + ipilimumab in comparison with pemetrexed + platinum component for patients for whom pemetrexed + cisplatin or pemetrexed + carboplatin is a suitable treatment option concurring with treatment of physician's choice; some of them only for subgroups.

The positive effect in overall survival was only shown in patients with non-epithelioid tumour histology. For this reason, positive and negative effects are weighed separately for patients with epithelioid versus non-epithelioid tumour histology in the following text.

Patients with non-epithelioid tumour histology

On the side of positive effects, there is an indication of major added benefit in the outcome of overall survival for patients with non-epithelioid tumour histology. There is an additional hint of a minor added benefit for the outcome of health status. On the positive side, there are also hints of lesser harm with the extent "considerable" or "major" for individual specific severe AEs in the category of serious/severe side effects.

The positive effects are accompanied by negative effects in serious/severe side effects. There are hints of greater harm, some with the extent "major", for immune-related SAEs and immune-related severe AEs as well as individual specific SAEs/severe AEs.

No data are available for health-related quality of life.

Overall, the negative effects do not completely outweigh the advantage in overall survival, but result in a downgrading of the extent of added benefit. For patients with non-epithelioid tumour histology, there is therefore an indication of considerable added benefit.

Patients with epithelioid tumour histology

On the positive side, there is a hint of a minor added benefit for the outcome of health status for patients with epithelioid tumour histology. There are also hints of lesser harm with the extent "considerable" or "major" for individual specific severe AEs in the category of serious/severe side effects.

The positive effects are accompanied by negative effects in serious/severe side effects. There are hints of greater harm, some with the extent "major", for SAEs, immune-related SAEs and immune-related severe AEs as well as individual specific SAEs/severe AEs.

No data are available for health-related quality of life.

In summary, for patients with epithelioid tumour histology, there is no hint of added benefit of nivolumab + ipilimumab in comparison with pemetrexed + platinum component; an added benefit is therefore not proven.

The result of the assessment of the added benefit of nivolumab + ipilimumab in comparison with the ACT is summarized in Table 18.

Table 18: Nivolumab + ipilimumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of unresectable malignant pleural mesothelioma in adults	Treatment of physician's choice[b]	▪ Patients with epithelioid tumour histology[c]: added benefit not proven[d] ▪ Patients with non-epithelioid tumour histology[c]: indication of considerable added benefit[d]

a. Presented is the ACT specified by the G-BA.
b. Guidelines recommend the use of pemetrexed + cisplatin, pemetrexed + carboplatin or bevacizumab + cisplatin + pemetrexed. The drugs bevacizumab and carboplatin are not approved for the present therapeutic indication. There is a discrepancy between the drugs approved for the therapeutic indication and those recommended in the guidelines. In a clinical trial, the combination therapies of pemetrexed + cisplatin, pemetrexed + carboplatin and bevacizumab + cisplatin + pemetrexed are deemed suitable comparators.
c. For which pemetrexed + cisplatin or pemetrexed + carboplatin represents the suitable treatment of physician's choice.
d. Except for one patient, only patients with an ECOG PS of 0 or 1 were included in the CA209-743 study. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which, based on the results of the CA209-743 study, derived an indication of considerable added benefit for nivolumab + ipilimumab in comparison with the ACT, treatment of physician's choice, for all patients with unresectable malignant pleural mesothelioma regardless of tumour histology.

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.

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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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