Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Nivolumab (new therapeutic indication: malignant pleural mesothelioma, first-line, combination with Ipilimumab)

of 16 December 2021

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes, in particular, the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information, in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient nivolumab (Opdivo) was listed for the first time on 15 July 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 1 June 2021, nivolumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 29 June 2021, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5,

Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nivolumab with the new therapeutic indication (in combination with ipilimumab for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 October 2021, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of nivolumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nivolumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Nivolumab (Opdivo) in accordance with the product information

Opdivo in combination with ipilimumab is indicated for the first-line therapy of adult patients with unresectable malignant pleural mesothelioma.

Therapeutic indication of the resolution (resolution of 16 December 2021):

- see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with unresectable malignant pleural mesothelioma; first-line therapy

Appropriate comparator therapy:

- Therapy according to doctor's instructions

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

its worth in practical application, unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, in principle, have a marketing authorisation for the therapeutic indication
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant advantage shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. Pemetrexed in combination with cisplatin is approved for the first-line therapy of unresectable malignant pleural mesothelioma.

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy for the present therapeutic indication. This does not affect the implementation of radiotherapy as a palliative treatment option.

on 3. There are no relevant resolutions on medicinal applications or non-medicinal treatments.

on 4. The general state of medical knowledge in the present therapeutic indication was represented by a systematic search for guidelines and reviews of clinical studies.

Accordingly, the evidence in the present therapeutic indication is limited. Relevant Cochrane reviews or systematic reviews could not be identified, nor recommendations from national guidelines.

The present recommendations of international guidelines unanimously recommend the use of a combination chemotherapy consisting of pemetrexed and a platinum derivative for the first-line treatment of unresectable malignant pleural mesothelioma. In this regard, pemetrexed in combination with cisplatin is the only approved treatment option in the present therapeutic indication. However, according to the present guideline recommendations, carboplatin is a suitable alternative to cisplatin, as comparable results have been achieved with the combination of carboplatin and pemetrexed compared to the combination of cisplatin and pemetrexed. Accordingly, no clear preference for one of the two combination therapies can be derived from the available evidence. The choice of the platinum component (carboplatin or cisplatin) should be based on the different toxicity profiles of the two substances and the existing comorbidities in each case.

In addition, the present guidelines recommend the use of pemetrexed in combination with cisplatin and bevacizumab. According to the guidelines, this recommendation is based on the results of a randomised phase III study in which the combination therapy of bevacizumab, cisplatin and pemetrexed resulted in a survival benefit compared to cisplatin and pemetrexed. However, there was also a higher rate of side effects in the

bevacizumab arm. In the present guidelines, these two combination therapies are predominantly recommended as equivalent therapies. Data on combination therapy with bevacizumab, carboplatin and pemetrexed are insufficient and no recommendations are available in these guidelines.

In summary, the combinations of active ingredients cisplatin and pemetrexed, carboplatin and pemetrexed, and cisplatin, pemetrexed, and bevacizumab may be considered for the first-line therapy of unresectable malignant pleural mesothelioma in adults. It should be noted that carboplatin and bevacizumab are not approved for the present therapeutic indication. Therefore, there is a discrepancy between the medicinal products approved in the indication and those recommended in the guidelines. Accordingly, a therapy according to the doctor's instructions is determined as the appropriate comparator therapy.

According to the guideline recommendations, the combinations of active ingredients cisplatin and pemetrexed, carboplatin and pemetrexed as well as cisplatin, pemetrexed and bevacizumab can be considered in the context of therapy according to the doctor's instructions. However, the possibility of the off-label use of the active ingredients mentioned in a clinical study does not allow any conclusions to be drawn about their appropriateness in the off-label use in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V. This does not affect an off-label prescription in specific cases according to the criteria of the established case law of the Federal Social Court on off-label use not regulated in the Pharmaceuticals Directive.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab in combination with ipilimumab is assessed as follows:

a) Adult patients with unresectable malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

An additional benefit is not proven.

b) Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy

Indication of a considerable additional benefit.

Justification:

The pharmaceutical company submitted data from the open-label, randomised, controlled phase III CA209-743 study, comparing nivolumab in combination with ipilimumab versus pemetrexed in combination with cisplatin or pemetrexed in combination with carboplatin for the benefit assessment.

Adult patients with untreated, unresectable malignant pleural mesothelioma and an ECOG-PS of zero to one were enrolled in the study, regardless of PD-L1 expression. For enrolment in

the study, the tumour tissue of the patients had to be determined histologically (epithelioid vs non-epithelioid tumour histology). Patients with undetermined tumour histology were excluded from the study. A total of 605 patients were enrolled and randomised in a 1:1 ratio to treatment with either nivolumab in combination with ipilimumab (intervention arm; N = 303) or pemetrexed in combination with cisplatin or pemetrexed in combination with carboplatin (comparator arm; N = 302). Randomisation was stratified by tumour histology (epithelioid vs non-epithelioid) and gender (female vs male).

In the intervention arm, treatment with nivolumab followed a weight-based dosing scheme (3 mg/kg body weight every 2 weeks), whereas the marketing authorisation requires administration at a fixed dosage (360 mg every 3 weeks), regardless of body weight. However, in line with the EMA, equivalence of the two dosing schemes is assumed for the present assessment. The treatment with ipilimumab was carried out according to the requirements in the product information. In case of discontinuation of ipilimumab therapy due to toxicity, treatment with nivolumab could be continued. In contrast, discontinuation of nivolumab therapy also required discontinuation of ipilimumab treatment. In the comparator arm, the use of pemetrexed in combination with cisplatin or pemetrexed in combination with carboplatin generally followed the requirements in the product information or the recommendations of guidelines.

Treatment was given in both study arms until disease progression, unacceptable toxicity, discontinuation of therapy, or reaching the maximum treatment duration. Under certain conditions, treatment could be continued in the intervention arm even after disease progression at the principal investigator's discretion. A changeover to the treatment of the other study arm was not planned.

The primary endpoint of the CA209-743 study was overall survival. Other patient-relevant endpoints were assessed in the categories of morbidity and side effects.

This assessment is based on the results of the data cut-off of 3 April 2020.

Implementation of the appropriate comparator therapy

According to the guideline recommendations, the combinations of active ingredients cisplatin and pemetrexed, carboplatin and pemetrexed as well as cisplatin, pemetrexed and bevacizumab can be considered in the context of therapy according to the doctor's instructions. In the comparator arm of the CA209-743 study, treatment was with pemetrexed in combination with cisplatin or pemetrexed in combination with carboplatin. Thus, no comparison is available versus cisplatin in combination with pemetrexed and bevacizumab. In particular, in light of the statements of clinical experts in the present procedure on the significance of the combination of cisplatin, pemetrexed and bevacizumab in the German health care context, adequate implementation of the appropriate comparator therapy is assumed on the whole.

Extent and probability of the additional benefit

Analysis across endpoints

In the subgroup analyses of the characteristic "tumour histology" (epithelioid vs non-epithelioid), significantly different effects were shown for the endpoints of overall survival, health status and serious adverse events (SAE) depending on the tumour histology. Thus, this effect modification of the characteristic "tumour histology" occurs consistently in several

endpoints relevant for the present assessment. In the present therapeutic indication, the histology of the tumour represents a relevant prognostic factor, with the epithelioid subtype having the comparatively most favourable prognosis[2]. Histological subtyping is recommended if biopsy is possible[3].

Against this background, the G-BA considers it appropriate to conduct a separate assessment of the additional benefit for patients with epithelial tumour histology and patients with non-epithelial tumour histology on the basis of the effect modification that occurred with regard to the characteristic "tumour histology".

In their statements, clinical experts in the present procedure stated that uncertainties must be assumed in the histological differentiation of mesotheliomas into the subtypes epithelioid, sarcomatoid and biphasic. Accordingly, the transitions between these subtypes are pathologically mostly fluid and do not allow a clear subtyping or often no subtyping at all is possible in the patients, if only a cytology from the pleural effusion is available.

However, in the view of the G-BA, these uncertainties in the histological diagnosis and differentiation of mesothelioma in clinical practice, which are comprehensible to the G-BA on the basis of the statements by the clinical experts, do not preclude a separate assessment of the additional benefit on the basis of the histologies investigated in the CA209-743 study (epithelioid and non-epithelioid). In this regard, the present assessment specifically focuses on the histological differentiation as performed for the CA209-743 study.

In the CA209-743 study, patients with indeterminable tumour histology were excluded from the study.

Mortality

For the endpoint of overall survival, there was a statistically significant difference between the treatment arms to the advantage of nivolumab in combination with ipilimumab in the total population of the CA209-743 study.

In the subgroup analyses for the endpoint of overall survival, there was an effect modification by the characteristic "tumour histology" (epithelioid vs non-epithelioid; p = 0.003).

For patients with non-epithelioid tumour histology, there is a statistically significant difference to the advantage of nivolumab in combination with ipilimumab. For these patients, there is an prolongation in survival time, which is assessed as a significant improvement in terms of extent.

For patients with epithelioid tumour histology, however, there was no statistically significant difference between the treatment arms. An additional benefit for this patient group is therefore not proven for overall survival.

[2] Scherpereel A, Opitz I, Berghmans T, Psallidas I, Glatzer M, Rigau D, Astoul P, Bölükbas S, Boyd J, Coolen J, De Bondt C, De Ruysscher D, Durieux V, Faivre-Finn C, Fennell D, Galateau-Salle F, Greillier L, Hoda MA, Klepetko W, Lacourt A, McElnay P, Maskell NA, Mutti L, Pairon JC, Van Schil P, van Meerbeeck JP, Waller D, Weder W, Cardillo G, Putora PM. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. Eur Respir J. 2020 Jun 11;55(6):1900953.

[3] Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S; ESMO Guidelines Committee. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v31-9.

Morbidity

Health status (EQ-5D, visual analogue scale)

The health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

Observation continued until death, end of study, or withdrawal of informed consent. In the intervention arm, patients continued to be observed beyond disease progression until study discontinuation. In the comparator arm, patients entered the follow-up phase if disease progression occurred (EQ-5D VAS assessment: 30 and 120 days after the last dose of study medication and every 3 months during the first year of survival follow-up, then every 6 months).

For the benefit assessment, the pharmaceutical company submits responder analyses for time to deterioration by ≥ 7, ≥ 10, and ≥ 15 points of VAS score from baseline.

According to IQWiG's current methodological approach (Methods 6.0, published on 5 November 2020), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) to be necessary for patient-reported endpoints to represent a noticeable change with sufficient certainty. For the EQ-5D VAS, the G-BA has recognised response thresholds of ≥ 7 and ≥ 10 points as a clinically relevant change in previous benefit assessment procedures in the present indication. Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% (here ≥ 15 points) and the responder analyses with a response threshold of ≥ 7 and ≥ 10 points are used to assess the additional benefit.

Based on the total population of the CA209-743 study, all three responder analyses (≥ 7, ≥ 10 and ≥ 15 points) showed a statistically significant difference to the advantage of nivolumab in combination with ipilimumab.

In the subgroup analyses for the endpoint of health status for responder analysis ≥ 7 points, there is an effect modification by the characteristic "tumour histology" (epithelioid vs non-epithelioid; p = 0.005).

For patients with non-epithelioid tumour histology, there is a statistically significant difference to the advantage of nivolumab in combination with ipilimumab. For patients with epithelioid tumour histology, there is no statistically significant difference between the treatment arms. Subgroup analyses on response thresholds ≥ 10 and ≥ 15 points were not reported by the pharmaceutical company. However, in the present data situation, it is assumed that, just as with the response threshold of ≥ 7 points, there is effect modification by the tumour histology characteristic.

LCSS-Meso ASBI

The patients' symptomatology was assessed using the Lung Cancer Symptom Scale - Mesothelioma Adaptation (LCSS-Meso).

Observation was conducted in the comparator arm until disease progression and in the intervention arm until the end of treatment. Follow-up was scheduled 30 and 120 days after the last dose of study medication for both study arms. Thus, there are differences between the treatment arms in terms of the observation planned for the patients. However, these are not considered serious enough to call into question the usability of the results, as the clear majority of patients in the intervention arm (61%) had discontinued treatment due to disease

progression, and the criterion for LCSS-Meso survey discontinuation for these patients is therefore the same as the criterion in the comparator arm.

The LCSS-Meso survey contains eight items, five of which relate to symptoms (loss of appetite, fatigue, cough, dyspnoea and pain) with the Average Symptom Burden Index (ASBI) as the mean of these five items. The LCSS-Meso ASBI illustrates the symptomatology in patients with malignant pleural mesothelioma and is used for the present benefit assessment.

There is a statistically significant advantage of nivolumab in combination with ipilimumab considering a response threshold of ≥ 15 points for time to deterioration of the LCSS-Meso ASBI.

Overall, in the endpoint category of morbidity for patients with epithelioid tumour histology, there is an advantage of nivolumab in combination with ipilimumab with regard to symptomatology. Patients with non-epithelioid tumour histology have advantages in terms of both symptomatology and health status.

Quality of life

No health-related quality of life data were collected in the CA209-743 study.

The pharmaceutical company assigns the remaining three items of the LCSS-Meso survey (symptom burden, activity impairment and general health-related quality of life) to health-related quality of life. However, these items are inappropriate to represent the complex construct of the health-related quality of life.

Side effects

Adverse events (AEs) in total

Nearly all patients in the CA209-743 study experienced an adverse event. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAE)

For the endpoint of SAE, there is a statistically significant difference to the disadvantage of nivolumab in combination with ipilimumab in the total population of the CA209-743 study.

The subgroup analyses for the endpoint of SAE showed an effect modification by the characteristic "tumour histology" (epithelioid vs non-epithelioid; p = 0.031).

For patients with non-epithelioid tumour histology, there is no statistically significant difference between the treatment arms. For patients with epithelioid tumour histology, there is a statistically significant difference to the clear disadvantage of nivolumab in combination with ipilimumab.

Severe AEs (CTCAE grade ≥ 3)

There was no statistically significant difference between the treatment arms for the endpoint of severe AEs (CTCAE grade ≥ 3).

Therapy discontinuations due to AEs

With regard to the endpoint of therapy discontinuations due to AEs (discontinuation of at least one active ingredient component), there was no statistically significant difference between the treatment arms.

Specific AEs

In detail, specific adverse events show statistically significant differences to the advantage of nivolumab in combination with ipilimumab with respect to nausea (PT, AEs), asthenia (PT, severe AEs), anaemia (PT, severe AEs), neutropenia (PT, severe AEs) and thrombocytopenia (PT, severe AEs). There are statistically significant differences to the disadvantage of nivolumab in combination with ipilimumab regarding immune-mediated SAEs, immune-mediated severe AEs (CTCAE grade ≥ 3), diarrhoea (PT, AEs), endocrine disorders (SOC, SAEs), elevated lipase (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]). For patients with epithelioid tumour histology, there was also a statistically significant difference to the disadvantage of nivolumab in combination with ipilimumab for renal and urinary disorders (SOC, SAEs).

In summary, the side effects for patients with epithelioid tumour histology show a clear disadvantage for nivolumab in combination with ipilimumab for the endpoint of SAE. For patients with non-epithelioid tumour histology, there is no statistically significant difference in this regard. There are no statistically significant differences in patients with epithelioid tumour histology and patients with non-epithelioid tumour histology with regard to the endpoints of severe AEs (CTCAE grade ≥ 3) and therapy discontinuations due to AEs. In detail, the specific AEs show both positive and negative effects of nivolumab in combination with ipilimumab compared to the appropriate comparator therapy.

Overall assessment

Results of the CA209-743 study on overall survival, morbidity and side effects are available for the benefit assessment of nivolumab in combination with ipilimumab for the first-line treatment of unresectable malignant pleural mesothelioma in adults.

In the subgroup analyses of the characteristic "tumour histology" (epithelioid vs non-epithelioid), significantly different effects were shown for the endpoints of overall survival, health status and serious adverse events (SAE) depending on the tumour histology. Thus, this effect modification of the characteristic "tumour histology" occurs consistently in several endpoints relevant for the present assessment. In the present therapeutic indication, the histology of the tumour represents a relevant prognostic factor, with the epithelioid subtype having the comparatively most favourable prognosis. Against this background, the G-BA considers it appropriate to conduct a separate assessment of the additional benefit for patients with epithelial tumour histology and patients with non-epithelial tumour histology on the basis of the effect modification that occurred with regard to the characteristic "tumour histology".

a) Adult patients with unresectable malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms in the group of patients with epithelioid tumour histology. With regard to overall survival, an additional benefit of nivolumab in combination with ipilimumab is therefore not proven.

In the endpoint category of morbidity, there is a statistically significant difference in symptomatology (LCSS-Meso ASBI) to the advantage of nivolumab in combination with ipilimumab.

With regard to health-related quality of life, no data were collected in the CA209-743 study.

In terms of side effects, nivolumab in combination with ipilimumab showed a statistically significant disadvantage in the endpoint of SAE. There were no statistically significant differences for the endpoints of severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs (discontinuation of at least 1 active ingredient component). In detail, the specific AEs show both positive and negative effects of nivolumab in combination with ipilimumab compared to the appropriate comparator therapy.

In the overall assessment, the positive effect of an improvement in the symptomatology is thus offset by a clear disadvantage in the case of SAEs.

In a weighing decision, the G-BA states that an additional benefit of nivolumab in combination with ipilimumab is not proven for the first-line treatment of unresectable malignant pleural mesothelioma in adults with epithelioid tumour histology, compared to the appropriate comparator therapy.

b) Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy

For the endpoint of overall survival, there is a statistically significant difference in the group of patients with non-epithelioid tumour histology to the advantage of nivolumab in combination with ipilimumab. Compared to the appropriate comparator therapy, nivolumab in combination with ipilimumab leads to a prolongation of survival time, which is assessed as a significant improvement in terms of extent.

In the endpoint category of morbidity, there are statistically significant differences to the advantage of nivolumab in combination with ipilimumab with regard to symptomatology (LCSS-Meso ASBI) and for the endpoint of health status (EQ-5D VAS).

With regard to health-related quality of life, no data were collected in the CA209-743 study.

For side effects, there were no statistically significant differences in the endpoints of SAE, severe AE (CTCAE grade ≥ 3), and discontinuation due to AEs (discontinuation of at least 1 active ingredient component). In detail, there are statistically significant differences between the treatment arms in specific AEs alone, showing both positive and negative effects.

Therefore, in the overall assessment, the positive effects with regard to overall survival, symptomatology and health status are not offset by any disadvantages.

In conclusion, the G-BA identifies a considerable additional benefit of nivolumab in combination with ipilimumab for the first-line treatment of unresectable malignant pleural mesothelioma in adults with non-epithelioid tumour histology, compared to the appropriate comparator therapy.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of an open-label, randomised controlled study. The cross-endpoint risk of bias is rated as low for the study.

The endpoint-specific risk of bias for the endpoint of overall survival is also rated as low.

Due to the open-label study design and the resulting lack of blinding for subjective endpoint assessment, the results for symptomatology, health status and the endpoint of discontinuation due to AEs are considered to have potentially high risk of bias.

Overall, the available data basis is therefore subject to uncertainties. However, the uncertainties are not rated to be so high as to justify a downgrading of the reliability of the overall assessment. In particular, the risk of bias of the endpoint of overall survival is rated as low. Thus, the reliability of data for the additional benefit determined for the patient group b) is classified in the category “indication”.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Opdivo with the active ingredient nivolumab. The therapeutic indication assessed here is as follows:

“Opdivo in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.”

The appropriate comparator therapy was determined to be a therapy according to doctor's instructions. The combinations of active ingredients cisplatin and pemetrexed, carboplatin and pemetrexed as well as cisplatin, pemetrexed and bevacizumab can be considered in this context.

The pharmaceutical company submitted data from the open-label, randomised, controlled phase III CA209-743 study, comparing nivolumab in combination with ipilimumab versus pemetrexed in combination with cisplatin or pemetrexed in combination with carboplatin for the benefit assessment.

Several endpoints show effect modification by the characteristic "tumour histology". Based on these effect modifications, the following patient populations result:

a) Adult patients with unresectable malignant pleural mesothelioma and epithelioid tumour histology; first-line therapy

and

b) Adult patients with unresectable malignant pleural mesothelioma and non-epithelioid tumour histology; first-line therapy

On patient population a)

For the endpoint of overall survival, there was no statistically significant difference between the treatment arms in the group of patients with epithelioid tumour histology.

In the morbidity category, nivolumab in combination with ipilimumab showed an advantage with regard to symptomatology.

With regard to health-related quality of life, no data were collected in the CA209-743 study.

In terms of side effects, there is a statistically significant difference to the clear disadvantage of nivolumab in combination with ipilimumab for the endpoint of SAE.

In the overall assessment, the positive effect on symptomatology is thus offset by a clear disadvantage in the case of SAEs. As a result, an additional benefit of nivolumab in combination with ipilimumab versus the appropriate comparator therapy is therefore not proven.

On patient population b)

For the endpoint of overall survival, there is a statistically significant effect to the advantage of nivolumab in combination with ipilimumab, which is assessed as a significant improvement.

In the morbidity category, nivolumab in combination with ipilimumab showed advantages with regard to symptomatology and the endpoint of health status.

With regard to health-related quality of life, no data were collected in the CA209-743 study.

There were no differences relevant to the assessment of the side effects.

In the overall assessment, the G-BA found a considerable additional benefit for nivolumab in combination with ipilimumab compared with the appropriate comparator therapy.

Despite existing uncertainties resulting from the open-label study design, the reliability of data of the additional benefit identified can be classified in the "indication" category, in particular due to the low risk of bias for the endpoint of overall survival.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company. The procedure of the pharmaceutical company is mathematically and methodologically largely comprehensible. Uncertainties arise mainly from the fact that the source used by the pharmaceutical company to determine the percentage of patients with unresectable malignant pleural mesothelioma is not restricted to exclusively malignant pleural mesothelioma. In this regard, it remains unclear whether the percentage of patients with unresectable malignant pleural mesothelioma differs from the corresponding percentage including all malignant mesotheliomas. Overall, it is assumed that the number of patients in the SHI target population is of a largely plausible magnitude.

No separate calculations are available with regard to a subdivision of the number of patients in the target population into patients with epithelioid tumour histology and patients with non-epithelioid tumour histology.

According to the dossier[4], the frequency of subtypes varies, with 50-60% of tumours having epithelioid histology and 10-20% having sarcomatoid histology. Accordingly, 25-35% are mixed forms. In the present CA209-743 study, the percentage of patients with epithelioid tumour histology was 78%, while the percentage of patients with non-epithelioid tumour histology was 22%.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 10 November 2021):

[4] Module 3 N; nivolumab - first-line therapy of unresectable malignant pleural mesothelioma in adults, 29.06.2021

https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf

Treatment with nivolumab in combination with ipilimumab may only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of adult patients with lung cancer or malignant pleural mesothelioma, as well as specialists in internal medicine and pulmonology or specialists in pulmonary medicine and doctors from other specialist groups participating in the Oncology Agreement.

In accordance with the Medicines Agency requirements regarding additional risk minimisation measures, the pharmaceutical company must provide healthcare professionals and patients with a patient card. The patient card contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with nivolumab as well as on infusion-related reactions. The prescribing doctor must discuss the risks of therapy with nivolumab with the patient. The patient card should be made available to the patient.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2021).

According to the product information of nivolumab, the recommended dosage of nivolumab in combination therapy with ipilimumab is 360 mg every 21 days, and the dosage of ipilimumab is 1 mg/kg every 42 days.

According to the product information of pemetrexed, the recommended dosage of pemetrexed is 500 mg/m² body surface area (BSA) every 21 days, and the dosage of cisplatin is 75 mg/m² BSA also every 21 days.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed:				
Nivolumab	1 x per 21-day cycle	17.4	1	17.4
+ Ipilimumab	1 x per 42-day cycle	8.7	1	8.7
Appropriate comparator therapy				
Patient population a) and b)				
Therapy according to doctor's instructions: - Cisplatin in combination with pemetrexed[5]				
Cisplatin	1 x per 21-day cycle	17.4	1	17.4
Pemetrexed	1 x per 21-day cycle	17.4	1	17.4

Consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

For dosages depending on body weight or body surface, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916).[6]

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					

[5] Costs are presented only for cisplatin in combination with pemetrexed. In addition, carboplatin in combination with pemetrexed and cisplatin in combination with pemetrexed and bevacizumab are also suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, carboplatin and bevacizumab are not approved in the present therapeutic indication and therefore no costs are represented for these regimens.

[6] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Nivolumab	360 mg	360 mg	2 x 100 mg + 4 x 40 mg	17.4	34.8 x 100 mg + 69.6 x 40 mg
+ Ipilimumab	1 mg/kg BW = 77 mg	77 mg	2 x 50 mg	8.7	17.4 x 50 mg
Appropriate comparator therapy					
Patient population a) and b)					
Therapy according to doctor's instructions: - Cisplatin in combination with pemetrexed[5]					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	17.4	17.4 x 100 mg + 17.4 x 50 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg

Costs:

Costs of the medicinal products:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed:					
Nivolumab 40 mg	4 ml CIS	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Nivolumab 100 mg	10 ml CIS	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Ipilimumab 50 mg	10 ml CIS	€ 3,849.07	€ 1.77	€ 216.54	€ 3,630.76
Appropriate comparator therapy					
Patient population a) and b)					

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Therapy according to doctor's instructions: - Cisplatin in combination with pemetrexed[5]					
Cisplatin 50 mg	50 ml CIS	€ 47.43	€ 1.77	€ 1.73	€ 43.93
Cisplatin 100 mg	100 ml CIS	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Pemetrexed 500 mg	500 mg PCI	€ 279.25	€ 1.77	€ 12.73	€ 264.75
Abbreviations: CIS = concentrate for the preparation of an infusion solution, PCI = Powder for concentrate for solution for infusion					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I to the Pharmaceuticals Directive (so-called OTC exception list) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
Appropriate comparator therapy							
Cisplatin							
Antiemetic treatment							

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates	Treatment days/ year	Costs/ patient/ year
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information does not provide any specific information why the necessary costs cannot be quantified.							
Hydration/ diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	17.4	€ 158.51
Sodium chloride 0.9% infusion solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 - € 263.11
	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		
Pemetrexed							
Dexamethasone[7] 2 x 4 mg	100 TAB 4 mg	€ 79.27	€ 1.77	€ 5.40	€ 72.10	52.2	€ 75.27
Folic acid: 350 - 1,000 µg/day[8]	100 x 400 µg TAB	€ 16.21	€ 0.81	€ 2.36	€ 13.04	365	€ 47.60 - € 95.19
Vitamin B12[7] 1,000 µg/day, every 3 cycles	10 x 1,000 µg SFI	€ 7.40	€ 0.37	€ 0.33	€ 6.70	5.8	€ 3.89
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; INF = infusion solution; TAB = tablets							

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations

[7] Fixed reimbursement rate

[8] The cost calculation for folic acid is based on the single dose of 400 µg of the non-divisible tablets available for cost calculation related to a dose range of 400 - 800 µg per day, even if a dose range of 350 - 1000 µg is given in the product information.

containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 10 September 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 June 2021 the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 1 July 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 September 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 October 2021. The deadline for submitting written statements was 22 October 2021.

The oral hearing was held on 8 November 2021.

By letter dated 9 November 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 26 November 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 December 2021, and the proposed resolution was approved.

At its session on 16 December 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	10 September 2019	Determination of the appropriate comparator therapy
Working group Section 35a	3 November 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	8 November 2021/ 9 November 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17 November 2021 1 December 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	7 December 2021	Concluding discussion of the draft resolution
Plenum	16 December 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 December 2021

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken