Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee 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 Ipilimumab (New therapeutic indication: Non-small cell lung cancer (NSCLC), combination with nivolumab and platinum-based chemotherapy, first-line treatment)

of 3 June 2021

Contents

1. Legal basis 2

2. Key points of the resolution 2

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy 3

2.1.1 Approved therapeutic indication of ipilimumab (Yervoy) in accordance with the product information 3

2.1.2 Appropriate comparator therapy 3

2.1.3 Extent and probability of the additional benefit 8

2.1.4 Summary of the assessment 14

2.2 Number of patients or demarcation of patient groups eligible for treatment . 16

2.3 Requirements for a quality-assured application 16

2.4 Treatment costs 17

3. Bureaucratic cost calculation 29

4. Process sequence 29

1. Legal basis

According to Section 35a, paragraph 1 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 trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first submission 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 benefits,
3. Additional medical benefit of the medicinal product in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Costs of therapy for the statutory health insurance,
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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient ipilimumab (Fycompa) was listed for the first time in the Große Deutsche Spezialitäten-Taxe (Lauer-Taxe) on 15 July 2015.

On 5 November 2020, Yervoy 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 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 December 2008, p. 7).

On 2 December 2020, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 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 ipilimumab with the new therapeutic indication (in combination with nivolumab and 2 cycles of platinum-based chemotherapy as first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation).

The G-BA commissioned IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2021 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. An oral hearing was also held.

The G-BA came to a resolution on whether an additional benefit of ipilimumab 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, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the G-BA on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA has assesses 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 ipilimumab.

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 ipilimumab (Yervoy) in accordance with the product information

Yervoy in combination with nivolumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours do not have a sensitising EGFR mutation or ALK translocation.

Therapeutic indication of the resolution (resolution of 3/6/2021):

see therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment

Appropriate comparator therapy:

- Pembrolizumab as monotherapy

[1] General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

b) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of <50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment

Appropriate comparator therapy:

- Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))

or

- Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceutical Directive

or

- Carboplatin in combination with nab-paclitaxel

or

- Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology)

or

- Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)

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 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, principally, 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 patient-specific benefit has already been determined by the Federal Joint Committee shall be preferred.
4. The comparator therapy should be part of the appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge.

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

on 1. Based on the authorisation status, the following active ingredient are generally available for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) without a sensitising EGFR mutation or ALK translocation: cisplatin, docetaxel, gemcitabine, ifosfamide, mitomycin, paclitaxel, nab-paclitaxel, pemetrexed, vindesine, vinorelbine, entrectinib, crizotinib, dabrafenib, trametinib, bevacizumab, atezolizumab and pembrolizumab.

on 2. For the present therapeutic indication it is assumed that the patients have no indication for definitive local therapy. A non-medicinal treatment cannot be considered as a comparator therapy in this therapeutic indication. This does not affect the implementation of radiotherapy or surgery as a palliative treatment option.

on 3. Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Entrectinib (ROS1-positive NSCLC): Resolution of 18 February 2021
- Atezolizumab: Resolution of 2 April 2020
- Pembrolizumab: Resolution of 19 September 2019
- Pembrolizumab (PD-L1 Expression: TPS ≥ 50%): Resolution of 3 August 2017
- Dabrafenib (NSCLC with BRAF V600-mutation): Resolution of 19 October 2017
- Trametinib (NSCLC with BRAF V600-mutation): Resolution of 19 October 2017
- Crizotinib (ROS1-positive NSCLC): Resolution of 16 March 2017

Guidelines:
Section K of the Pharmaceuticals Directive, Annex VI - Off-label use, resolution of 18 October 2018: Carboplatin-containing medicinal products for advanced non-small cell lung cancer (NSCLC) - combination therapy

on 4. The generally accepted state of medical knowledge for the indication was established by means of a systematic search for guidelines and reviews of clinical studies.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

In first-line treatment, based on the available evidence on treatment options, PD-L1 expression is differentiated into two subpopulations with a PD-L1 expression cut-off value of 50% (TPS):

a) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment

Current guidelines recommend pembrolizumab monotherapy for first-line treatment of metastatic NSCLC when PD-L1 expression is ≥ 50%, regardless of histologic status. The corresponding benefit assessment of pembrolizumab, based on the KEYNOTE-024

study, showed an indication of a considerable additional benefit compared with platinum-based chemotherapy (resolution of 3 August 2017). Pembrolizumab significantly improved overall survival, delayed the onset of significant disease symptoms and severe adverse events (CTCAE grade ≥ 3) and showed beneficial effects on health-related quality of life. Therefore, pembrolizumab monotherapy represents a current standard of care and is determined to be an appropriate comparator therapy. Pembrolizumab is approved only for metastatic patients with TPS ≥ 50%.

Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy was evaluated by the G-BA for the patient group with PD-L1 expression of ≥ 50% (TPS) based on an adjusted indirect comparison versus pembrolizumab monotherapy by resolution of 19 September 2019 (non-squamous histology only). As the extent of the observed additional benefit in the endpoint overall survival could not be quantified for the entire subpopulation and an assessment of symptomatology and health-related quality of life was not possible, an additional benefit was determined, the extent of which cannot be quantified. Based on these data, pembrolizumab monotherapy compared to pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy is determined to be the sole appropriate comparator therapy.

For squamous NSCLC, the combination of pembrolizumab plus carboplatin and either paclitaxel or nab-paclitaxel is also approved for first-line use. For patients with PD-L1 expression ≥ 50% (TPS), no additional benefit over pembrolizumab monotherapy was identified by the G-BA in its resolution of 19 September 2019, as no suitable data were available for comparison with the appropriate comparator therapy. The value of this pembrolizumab combination in squamous NSCLC cannot be conclusively assessed at this time, and it is not currently considered an appropriate comparator therapy.

In addition, for non-squamous metastatic NSCLC, atezolizumab in combination with bevacizumab, paclitaxel and carboplatin is approved for first-line therapy. For patients with a PD-L1 expression ≥ 50% (TPS), no additional benefit was determined by the G-BA in its resolution of 2 April 2020, as no data were available for a comparison with the appropriate comparator therapy.

Atezolizumab is also approved in combination with nab-paclitaxel and carboplatin for the first-line treatment of non-squamous NSCLC. For patients with a PD-L1 expression ≥ 50% (TPS), no additional benefit was determined by the G-BA in its resolution of 2 April 2020, as no data were available for a comparison with the appropriate comparator therapy.

b) <u>Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of <50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment</u>

For patients with PD-L1 expression < 50% (TPS), platinum-based combination chemotherapy (cis- or carboplatin) with a third-generation cytostatic agent (vinorelbine, gemcitabine, docetaxel, paclitaxel, or pemetrexed) is a standard of care according to the available evidence. However, no preference for a particular combination can be inferred from the evidence. In contrast to cisplatin, carboplatin is not approved for the treatment of NSCLC, but can be prescribed for patients as an "off-label use" (see Annex VI to Section K of the Pharmaceutical Directive), whereby the

selection of the platinum component should be based on the different toxicity profile and existing comorbidities of the patients.

Nab-paclitaxel is approved in combination with carboplatin for the first-line treatment of NSCLC. In the guidelines, this combination is recommended in the present therapeutic indication, therefore the G-BA classifies nab-paclitaxel as a further appropriate therapy option for patients with a PD-L1 expression of < 50% (TPS).

In the benefit assessment, a hint of non-quantifiable additional benefit was declared for pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy in a resolution dated 19 September 2019. For patients with non-squamous NSCLC and PD-L1 expression of <50% (TPS), hint of non-quantifiable additional benefit over pemetrexed plus platinum-containing chemotherapy was identified based on a meta-analysis of two randomised controlled studies, Keynote-021G and Keynote-189. There was a benefit in the endpoint overall survival, the extent of which was non-quantifiable due to available subgroup analyses and their relevant uncertainties. In determining the present appropriate comparator therapy, it is taken into account that a meta-analysis of two randomised controlled trials forms the data basis for this subpopulation. Furthermore, clinical experts stated in the benefit assessments for atezolizumab (resolution of 2 April 2020) that pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy represents another standard of care. Therefore, the G-BA also considers this therapy option to be another appropriate therapy option in the present therapeutic indication for patients with squamous histology and a PD-L1 expression < 50% (TPS).

For pembrolizumab in combination with carboplatin and (nab-)paclitaxel, hint of considerable additional benefit for squamous NSCLC was stated in the benefit assessment resolution dated 19 September 2019. For patients with a PD-L1 expression of < 50% (TPS), hint for a considerable additional benefit over (nab-)paclitaxel based on the advantage in the endpoint of overall survival was pronounced on the basis of the KEYNOTE 407 study. Currently, the guidelines identified in the search and synopsis of evidence do not yet provide a clear or unanimous recommendation for the use of the aforementioned combination therapy. However, in view of the positive treatment effects of the combination of pembrolizumab and carboplatin and either paclitaxel or nab-paclitaxel presented in the benefit assessment resolution, it is currently considered an appropriate comparator therapy (only in the case of squamous histology) for patients with PD-L1 expression < 50% (TPS).

For atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, no additional benefit was declared in the benefit assessment by resolution of 2 April 2020 compared with the appropriate comparator therapy for the first-line treatment of metastatic non-squamous NSCLC in patients with a PD-L1 expression of < 50% (TPS), as there were no usable data for a comparison with the appropriate comparator therapy.

For atezolizumab in combination with nab-paclitaxel and carboplatin, no additional benefit over nab-paclitaxel and carboplatin for the first-line treatment of metastatic non-squamous NSCLC in patients with PD-L1 expression of <50% (TPS) was declared in the benefit assessment resolution of 2 April 2020. Overall, there were no statistically significant differences for the endpoint categories overall survival, morbidity and quality of life. The disadvantages for atezolizumab in combination with nab-paclitaxel and carboplatin for severe AE (CTCAE grade 3-4) were considered to be significant for patients. Atezolizumab in combination with nab-paclitaxel is therefore not considered an appropriate comparator therapy.

Since ipilimumab is used in combination with nivolumab and 2 cycles of platinum-based combination chemotherapy in the present therapeutic indication, monochemotherapies cannot be considered as an appropriate comparator therapy.

In the overall review, the G-BA determined cisplatin or carboplatin in combination with a third-generation cytostatic agent or pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy or pembrolizumab in combination with carboplatin and either paclitaxel or nab-Paclitaxel (for patients with squamous histology only) were determined to be equally appropriate comparators.

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 ipilimumab in combination with nivolumab and platinum-based chemotherapy is assessed as follows:

a) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment

An additional benefit is not proven.

Justification:

The pharmaceutical company does not submit any data for the assessment of the additional benefit as she could not identify any suitable studies for a comparison with the appropriate comparator therapy. An assessment of the additional benefit is not possible data basis. Therefore, an additional benefit is not proven.

b) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of <50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment

Hint for a minor additional benefit

Justification:

For the benefit assessment, the pharmaceutical company draws on the results of the open-label, randomised, controlled, multicentre CA209-9LA study, which has been ongoing since August 2017 and compares ipilimumab in combination with nivolumab and platinum-based chemotherapy with platinum-based chemotherapy. The CA209-9LA study is being conducted in 103 study sites in Asia, Australia, Europe, North and South America.

The study included adult patients with stage IV squamous and non-squamous NSCLC without EGFR mutation or ALK translocation with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1 regardless of Programmed Cell Death Ligand (PD-L1) expression. The inclusion criteria of the CA209-9LA study additionally included patients in

stage IIIB without the possibility of curative therapy. However, this was true for only 2% of the included patients. Prior systemic therapy for stage IIIB or IV NSCLC was not allowed. Patients with brain metastases were excluded from the study. Patients with treated brain metastases were eligible for inclusion if neurologic symptoms had regressed to baseline at least 2 weeks before inclusion in the study and patients were either not receiving corticosteroids or were receiving a stable or decreasing dose of <10 mg prednisone equivalent per day.

A total of 719 patients were enrolled in the CA209-9LA study and randomised in a 1:1 ratio to treatment with either ipilimumab in combination with nivolumab and platinum-based chemotherapy (N = 361) or platinum-based chemotherapy alone (N = 358). The type of chemotherapy was dependent on the histology of the tumour: Patients with squamous histology received carboplatin in combination with paclitaxel. Patients with non-squamous histology received either cisplatin or carboplatin in combination with pemetrexed. The choice of platinum component was made by the principal investigator prior to randomisation on the basis of suitability criteria.
Randomisation was stratified by PD-L1 expression (≥ 1% vs < 1%), tumour histology (squamous histology vs non-squamous histology), and sex (male vs female). Patients with non-quantifiable PD-L1 status (tumours with unmeasurable PD-L1 expression or insufficient sample quality for PD-L1 expression determination) were assigned to the population with PD-L1 expression < 1% for stratification. The therapy with ipilimumab as well as nivolumab corresponds to the requirements in the product information. The maximum treatment duration for ipilimumab + nivolumab is 24 months.
In the comparator arm, up to 4 cycles of platinum-based chemotherapy were administered, after which patients with squamous histology and no disease progression could receive maintenance treatment with pemetrexed starting at cycle 5.
Treatment was given until disease progression (determined by Response Evaluation Criteria-In-Solid-Tumours [RECIST] criteria version 1.1), unacceptable intolerance, withdrawal of consent, or reaching the maximum treatment duration. Under certain conditions, treatment could be continued after disease progression at the principal investigator's discretion. Switching patients from the comparator arm to treatment with ipilimumab in combination with nivolumab after disease progression was not permitted.
The primary endpoint of the CA209-9LA study was overall survival. Secondary patient-specific endpoint were assessed in the categories of morbidity and side effects.

Patients were followed endpoint-specifically, maximally until death, withdrawal of consent, or study termination.

For the benefit assessment, the second data cut-off from 9 March 2020 was used, which corresponds to the a priori planned final analysis for overall survival. The analysis was scheduled after 402 events.

About the study population

The median age of the patients included in the CA209-9LA study was 65 years, only a few patients with an age of 75 years or older were included, and the general condition was good or very good (ECOG performance status 0-1) according to the inclusion criteria of the study. The median age in the target population of patients with NSCLC, according to the EPAR

(footnote: EPAR p. 155), on the other hand, at 71 years. According to the SmPC, data from elderly patients (≥ 75 years) from the CA209-9LA study are limited (see product information section 5.1). In these patients, ipilimumab in combination with nivolumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk in each individual case. This was also pointed out by the medical societies in their statements on the present benefit assessment resolution.

Relevant subpopulation of study CA209-9LA - PD-L1 status

For the benefit assessment, the pharmaceutical company uses a subpopulation of the CA209-9LA study. These are patients with metastatic, non-squamous or squamous NSCLC whose tumours have PD-L1 expression < 50% (N = 497). Patients with non-quantifiable PD-L1 expression (tumours with unmeasurable PD-L1 expression or insufficient sample quality for PD-L1 expression determination) were not included in the subpopulation.

For the implementation of the appropriate comparator therapy and the use of carboplatin according to the Pharmaceuticals Directive

Carboplatin is only approved in combination with nab-paclitaxel for the first-line treatment NSCLC, but not in combination with other third-generation cytostatics. According to the current version of Annex VI to Section K of the Pharmaceuticals Directive, carboplatin can be prescribed off-label in patients with advanced NSCLC. According to the determination of the appropriate comparator therapy, carboplatin in combination with third-generation cytostatic agents is an equally appropriate comparator therapy. The appropriate comparator therapy is therefore adequately implemented in the CA209-9LA study.

Extent and probability of the additional benefit

Mortality

The overall survival endpoint in the CA209-9LA study is defined as the time between the date of randomisation and the date of death from any cause.

For the endpoint overall survival, there is a statistically significant difference in favour of ipilimumab in combination with nivolumab and platinum-based chemotherapy. The extent of overall survival prolongation achieved is assessed as a significant improvement in benefit over platinum-based chemotherapy.

There is an effect modification by the characteristic “adequately treated brain metastases at baseline (yes/no)” for overall survival. In both subgroups, a statistically significant effect to the advantage of ipilimumab in combination with nivolumab and platinum-based chemotherapy is seen, with a greater benefit seen in patients with adequately treated brain metastases receiving ipilimumab in combination with nivolumab and platinum-based chemotherapy.
This effect modification is not evident in any other patient-specific endpoint. The corresponding subgroup results are presented, but do not lead to any specific statements in this regard in the overall assessment.

Morbidity

Progression-free survival

Progression-free survival (PFS) is a secondary endpoint in the CA209-9LA study and was collected by an independent review committee (BIRC) according to RECIST v1.1 criteria. PFS is defined as time between randomisation and first date of documented progression or death.

In the intervention arm, therapy with ipilimumab in combination with nivolumab and platinum-based chemotherapy showed a significantly longer progression-free survival than in the comparator arm.

The PFS endpoint is a combined endpoint composed of endpoints of the "mortality" and "morbidity" categories. The "mortality" endpoint component is already assessed via the "overall survival" endpoint as an independent endpoint.

The morbidity component was not assessed based on symptom onset but solely by means of imaging procedures (radiologically determined disease progression according to the mRECIST v1.1 criteria). Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (LCSS-ABSI) and health status (EQ-5D Visual Analogue Scale)

Symptomatology will be assessed in the CA209-9LA study using the Average Symptom Burden Index of the Lung Cancer Symptom Scale questionnaire (LCSS-ASBI).

General health status is assessed using the EQ-5D visual analogue scale (EQ-5D-VAS). The LCSS-ASBI and the EQ-5D will be collected every 3 weeks after baseline for the first 6 months, then every 6 weeks during therapy, and if necessary at the time of follow-up. In addition, the EQ-5D questionnaire will be collected at subsequent survival visits (every 3 months in the 1st year of follow-up, and every 6 months thereafter).

In its written statements, the pharmaceutical company clarifies that the definition "time to permanent deterioration" refers to all further follow-up surveys, and that in each of these no improvement below the response threshold may occur. From his assessment presented with the statements, although for some patients a first-time deterioration is included as an event in the evaluations without further surveys, this is largely balanced between treatment arms and involves few events (LCSS-ASBI about 10%, EQ-5D VAS < 5%).

Symptomatology (LCSS-ABSI)

For the endpoint Symptomatology no statistically significant difference was detected between the treatment arms. An additional benefit of ipilimumab in combination with nivolumab and platinum-based chemotherapy for the endpoint symptomatology is therefore not proven.

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

For the benefit assessment, the pharmaceutical company submitted responder analyses for time to worsening by ≥ 7, ≥ 10, and ≥ 15 points of VAS score from baseline. The responder analysis with response criteria ≥ 7 and ≥ 10 were presented by IQWiG in the addendum appendix.

The study on which the derivation of the minimal important difference (MID) for the responder analysis is based (Pickard et al., 2007) is not considered by IQWiG to be appropriate for demonstrating the validity of the MID. This is justified on the one hand by the fact that the aforementioned work does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion to derive a valid MID. Furthermore, the anchors ECOG-PS and FACT-G sum score used in the study are also not considered by IQWiG to be appropriate for deriving a MID.

Against the background that the validation study in question has already been used in previous assessments, the G-BA uses the responder analyses with response criteria ≥ 7 points and ≥ 10 points to assess the effects on health status in the present assessment.

Here, regarding the response criteria ≥ 7 points and ≥10 points, a statistically significant difference in favour of ipilimumab in combination with nivolumab and platinum-based chemotherapy is shown. Regarding the response criterion ≥ 15 points, there is no statistically significant difference between the treatment groups.

Quality of life

Health-related quality of life was not assessed in the CA209-9LA study.

Side effects

Side effects were assessed in both treatment groups up to 100 days after the last dose of study medication.

Total adverse events (AEs)

Nearly all study participants experienced an adverse event. These are only presented in a supplementary manner.

Serious Adverse Events (SAEs)

For the endpoint SAEs, there was a statistically significant difference in the disadvantage of ipilimumab in combination with nivolumab and platinum-based chemotherapy compared to platinum-based chemotherapy.

Severe AE (CTCAE grade ≥ 3)

For the endpoint severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference to the disadvantage of ipilimumab in combination with nivolumab and platinum-based chemotherapy.

Discontinuation due to AEs (discontinuation of at least 1 combination of active ingredients)

Regarding the endpoint discontinuation due to AEs (discontinuation of at least 1 combination of active ingredients), there is a negative effect of ipilimumab in combination with nivolumab and platinum-based chemotherapy compared to platinum-based chemotherapy.

Specific AEs

Immune-mediated SAEs and severe AEs (CTCAE grade ≥ 3)

For the endpoints immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3), there is a statistically significant difference to the disadvantage of ipilimumab in combination with nivolumab and platinum-based chemotherapy.

Anaemia (PT, severe AEs [CTCAE grade ≥ 3])

Regarding the endpoint anaemia (severe AEs [CTCAE grade ≥ 3]), the details show a statistically significant difference to the benefit of ipilimumab in combination with nivolumab and platinum-based chemotherapy.

Lipase elevated (PT, severe AEs [CTCAE grade ≥ 3]), Amylase elevated (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), Skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]), Endocrine disorders (SOC, severe AEs [CTCAE grade ≥ 3])

In detail, consideration of the specific AEs for the endpoints lipase elevated (PT, severe AEs [CTCAE grade ≥ 3]), amylase elevated (PT, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), Skin and subcutaneous tissue disorders (SOC, severe AEs [CTCAE grade ≥ 3]) and endocrine disorders (SOC, severe AEs [CTCAE grade ≥ 3]) each showed a statistically significant difference to the disadvantage of ipilimumab in combination with nivolumab and platinum-based chemotherapy.

Based on the negative effects on SAEs, severe AEs (CTCAE grade ≥3) and treatment discontinuations due to AEs as well as in detail on immune-mediated SAEs and severe AEs (CTCAE grade ≥ 3 and other specific AEs ascertained, a relevant disadvantage of ipilimumab in combination with nivolumab and platinum-based chemotherapy compared to platinum-based chemotherapy with significant and for the patients burdening side effects can be established.

<u>Overall assessment</u>

For the assessment of the additional benefit of ipilimumab in combination with nivolumab and platinum-based chemotherapy, results from the open-label, randomised, controlled trial CA209-9LA are available for the subpopulation of patients with PD-L1 expression < 50% on the endpoint categories mortality, morbidity, and side effects compared to platinum-based chemotherapy.

In the mortality endpoint category, there is a statistically significant difference in favour of ipilimumab in combination with nivolumab and platinum-based chemotherapy. The extent of overall survival prolongation achieved is assessed as a significant improvement in benefit over platinum-based chemotherapy.

In the endpoint category morbidity, there was no statistically significant difference with regard to symptoms. For the endpoint health status, there is an advantage for ipilimumab in combination with nivolumab and platinum-based chemotherapy.

Health-related quality of life was not recorded in the CA209-9LA study. Statements on quality of life are given high priority, especially in advanced tumour diseases and palliative therapy situations.

With regard to side effects, relevant disadvantages of ipilimumab in combination with nivolumab and platinum-based chemotherapy compared to platinum-based chemotherapy were observed in the endpoints SAEs, severe AEs (CTCAE grade ≥3), discontinuation due to AEs as well as in detail for the specific AEs, with significant and distressing side effects for the patients.

In a weighing decision, the negative effects in side effects do not call into question the additional benefit due to the improvement in overall survival, but they do lead to a downgrading of the extent of additional benefit.

Overall, in the first-line treatment of patients with metastatic NSCLC without a sensitive EGFR-mutation or ALK translocation and PD-L1 expression < 50%, there is therefore evidence of a minor additional benefit for ipilimumab in combination with nivolumab and platinum-based chemotherapy compared to platinum-based chemotherapy.

Reliability of data (probability of additional benefit)

The reliability of the additional benefit identified is classified in the "indication" category. The risk of bias at the study level and of the endpoint overall survival is rated as low.

Results on patient-reported endpoints on symptomatology and health status are to be regarded as potentially highly biased and of limited significance due to the open study design and the resulting lack of blinding. However, the reduced certainty of results caused by this does not justify a downgrading of the reliability of the overall assessment of the additional benefit.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient ipilimumab.

"Yervoy is indicated in combination with nivolumab and 2 cycles of platinum-based chemotherapy for the first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumours lack a sensitising EGFR-mutation or ALK translocation."

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR-mutations or ALK translocations; first-line treatment

b) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of <50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment

Patient group a)

The appropriate comparator therapy was determined as follows:

- Pembrolizumab as monotherapy

The pharmaceutical company did not submit any data to prove the additional benefit. Thus, an additional benefit is not proven.

Patient group b)

The appropriate comparator therapy was determined as follows:

- Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))

or

- Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceutical Directive

or

- Carboplatin in combination with nab-paclitaxel

or

- Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology)

or

- Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)

For the assessment of the additional benefit of ipilimumab in combination with nivolumab and platinum-based chemotherapy, the pharmaceutical company presents results from the open-label, randomised, controlled phase III CA209-9LA study for the subpopulation of patients with PD-L1 expression < 50% on the endpoint categories mortality, morbidity and on side effects compared to platinum-based chemotherapy.

Regarding the endpoint category mortality, there is a statistically significant difference in favour of ipilimumab in combination with nivolumab and platinum-based chemotherapy. The extent of overall survival prolongation achieved is assessed as a significant improvement in benefit over platinum-based chemotherapy.

In the endpoint category morbidity, there was no statistically significant difference with regard to symptoms. For the endpoint health status, there is an advantage for ipilimumab in combination with nivolumab and platinum-based chemotherapy.

Health-related quality of life was not recorded in the CA209-9LA study.

Regarding side effects, there is a relevant disadvantage of ipilimumab in combination with nivolumab and platinum-based chemotherapy compared to platinum-based chemotherapy, with significant and distressing side effects for patients.

In a weighing decision, the negative effects in side effects do not call into question the additional benefit due to the improvement in overall survival, but they do lead to a downgrading of the extent of additional benefit.

The reliability of the additional benefit identified is classified in the “indication” category. The risk of bias at the study level and of the endpoint overall survival is rated as low.

Overall, in the first-line treatment of patients with metastatic NSCLC without a sensitive EGFR-mutation or ALK translocation and PD-L1 expression < 50%, there is therefore evidence of a minor additional benefit for ipilimumab in combination with nivolumab and platinum-based chemotherapy compared to platinum-based chemotherapy.

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).

For the number of German patients with lung cancer, only the incidence for 2020 (62,380 patients) is used as the basis for the calculations, as these are patients in first-line therapy, and it is therefore unlikely that the prevalent patients of previous years have not yet received first-line treatment.

The following calculation steps are used to narrow down this group of patients to the target population:

1. The proportion of lung cancer patients with NSCLC is 81.7% - 83.2% (50,976 - 51,903 patients).

2. Of these, 48.5% of patients are in stage IV (24,749 - 25,199 patients).

3. First-line therapy is given in 76.9% - 78.5% of cases (19,032 - 19,788 patients).

4. The proportion of patients without EGFR-mutation is 89.7% - 95.1%. The percentage of patients without ALK translocation is 96.1% - 98.0%. In total, the number is 16,329 - 18,423 patients without EGFR-mutation or ALK translocation.

5. The proportion of patients with stage IV NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) is 25.9%-28.9% (4,228-5,328 patients). The proportion of patients with stage IV NSCLC with PD-L1 expressing tumours (TPS) < 50% is 71.1% - 74.1% (12,101 - 13,095 patients).

6. Taking into account a proportion of patients insured by the SHI of 87.8%, this results in 14,343-16,183 patients in the target population. Thereof

6a 3714 - 4680 patients with stage IV NSCLC with PD-L1 expressing tumours (TPS ≥ 50%) and

6b. 10.630 - 11,503 patients with stage IV NSCLC with PD-L1 expression (TPS) < 50%.

Due to uncertainties regarding the data basis in the target population in Germany, both an overestimation and an underestimation of patient numbers are possible.

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: ipilimumab) at the following publicly accessible link (last access: 28 April 2021):

https://www.ema.europa.eu/documents/all-authorised-presentations/yervoy-epar-all-authorised-presentations_de.pdf

Treatment with ipilimumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology and specialists in internal medicine and pneumology or specialists participating in the Oncology Agreement who are experienced in the treatment of adult patients with non-small cell lung cancer.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide a patient card.

Data from elderly patients (≥ 75 years) from the CA209-9LA study are limited. In these patients, ipilimumab in combination with nivolumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk in each individual case.

2.4 Treatment costs

The treatment costs are based on the product information in the specialist information as well as the information in the Lauer-Taxe (last revised: 15 May 2021).

The (daily) doses recommended in the product information or the indicated publications were used as calculation basis.

According to the product information, the recommended dosage of nivolumab in combination therapy with ipilimumab plus 2 cycles of platinum-based chemotherapy is 360 mg every 21 days, and the dosage of ipilimumab is 1 mg/kg KG. After discontinuation of platinum-based chemotherapy, the use of ipilimumab in combination with nivolumab is continued.

The active ingredient ipilimumab is dosed depending on body weight. For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[2]

The recommended dosage for pembrolizumab in monotherapy is 200 mg every 3 weeks or 400 mg every 6 weeks. The three-week therapy schedule is used to calculate costs.

Cisplatin is dosed differently depending on the combination preparation. According to the product information of the combination preparations, the single dose of cisplatin in combination with vinorelbine or gemcitabine is 75 - 100 mg/m², in combination with docetaxel and pemetrexed 75 mg/m² and in combination with paclitaxel 80 mg/m².

For carboplatin, a cycle duration of 3 weeks is used. For the use of carboplatin in the off-label indication "combination therapy for advanced NSCLC", Annex VI of the Pharmaceutical Directive specifies the following dosage: up to 500 mg/m² or AUC 6.0. For the use of carboplatin in combination with nab-paclitaxel, a dosage of 500 mf/m2 is also used, according to the product information.

[2] https://www.gbe-bund.de/gbe10/pkg_isgbe5.prc_isgbe?p_uid=gast&p_aid=0&p_sprache=D

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 patient-individual 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.

The annual treatment costs shown refer to the first year of treatment.

Treatment duration:

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Medicinal product to be assessed				
Ipilimumab	Once per 42 day cycle	8.7 cycles	1	8.7
+ nivolumab	Once per 21 day cycle	17.4 cycles	1	17,4
+ 2 cycles of platinum-based chemotherapy				
Cisplatin	Once per 21 day cycle	2	1	2
Pemetrexed	Once per 21 day cycle	2	1	2
or				
Carboplatin	Once per 21 day cycle	2	1	2
Pemetrexed	Once per 21 day cycle	2	1	2
Paclitaxel	Once per 21 day cycle	2	1	2
Appropriate comparator therapy				
a) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR-mutations or ALK translocations; first-line treatment				

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Pembrolizumab	Once per 21 day cycle	17.4 cycles	1	17,4
b) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of <50% (PD-L1 expression) and without EGFR-mutations or ALK translocations; first-line treatment				
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))				
Cisplatin	Once per 21 day cycle	17.4 cycles	1	17.4
Docetaxel	Once per 21 day cycle	17.4 cycles	1	17,4
Gemcitabine	Once per 21 day cycle	17.4 cycles	2	34,8
Paclitaxel	Once per 21 day cycle	17.4 cycles	1	17,4
Pemetrexed	Once per 21 day cycle	17.4 cycles	1	17,4
Vinorelbine	Twice per 21 day cycle	17.4 cycles	2	34,8
Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceutical Directive				
Carboplatin	Once per 21 day cycle	17.4 cycles	1	17,4
Docetaxel	Once per 21 day cycle	17.4 cycles	1	17,4
Gemcitabine	Twice per 21 day cycle	17.4 cycles	2	34,8

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Paclitaxel	Once per 21 day cycle	17.4 cycles	1	17,4
Pemetrexed	Once per 21 day cycle	17.4 cycles	1	17,4
Vinorelbine	Twice per 21 day cycle	17.4 cycles	2	34,8
Carboplatin in combination with nab-paclitaxel				
Carboplatin	Once per 21 day cycle	17.4 cycles	1	17,4
nab-paclitaxel	3 x per 21 day cycle	17.4 cycles	3	52,2
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology)				
Pembrolizumab	Once per 21 day cycle	17.4 cycles	1	17,4
Pemetrexed	Once per 21 day cycle	17.4 cycles	1	17,4
Carboplatin	Once per 21 day cycle	17.4 cycles	1	17,4
Cisplatin	Once per 21 day cycle	17.4 cycles	1	17,4
Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)				
Pembrolizumab	Once per 21 day cycle	17.4 cycles	1	17,4
Carboplatin	Once per 21 day cycle	17.4 cycles	1	17,4

Name of therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Paclitaxel	Once per 21 day cycle	17.4 cycles	1	17,4
nab-paclitaxel	3 x per 21 day cycle	17.4 cycles	3	52,2

Consumption:

For the cost representation only the doses 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 (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average 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)[3].

Name of therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by strength/day of treatment	Treatment days/ Patient/ Year	Average annual consumption by strength
Medicinal product to be assessed					
Ipilimumab	1 mg/kg bw = 77 mg	77 mg	2 x 50 mg	8.7	17.4 x 50 mg
+ nivolumab	360 mg	360 mg	3 x 100 mg + 2 x 40 mg	17.4	52.2 x 100 mg + 34.8 x 40 mg
+ 2 cycles of platinum-based chemotherapy					
Cisplatin	75 mg/m² = 142.5 mg	142.5 mg	1 x 100 mg + 1 x 50 mg	2	2 x 100 mg + 2 x 50 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	2	4 x 500 mg
or					

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

Name of therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by strength/day of treatment	Treatment days/ Patient/ Year	Average annual consumption by strength
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	2	2 x 600 mg + 4 x 150 mg + 2 x 50 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	2	4 x 500 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	2	4 x 100 mg + 2 x 150 mg
Appropriate comparator therapy					
a) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of ≥ 50% (PD-L1 expression) and without EGFR-mutations or ALK translocations; first-line treatment					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17,4	34.8 x 100 mg
b) Adult patients with metastatic non-small cell lung cancer (NSCLC) with a tumour proportion score [TPS] of <50% (PD-L1 expression) and without EGFR mutations or ALK translocations; first-line treatment					
Cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology))					
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
	80 mg/m² = 152 mg	152 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	17,4	17.4 x 100 mg 17.4 x 50 mg + 17.4 x 10 mg
	100 mg/m² = 190 mg	190 mg	2 x 100 mg	17,4	34.8 x 100 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17,4	17.4 x 160 mg
Gemcitabine	1250 mg/m² =2375 mg	2375 mg	1 x 2000 mg + 2 x 200 mg	34.8	34.8 x 2000 mg + 69.6 x 200 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17,4	17.4 x 150 mg + 34.8 x 100 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17,4	34.8 x 500 mg
Vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	34,8	34.8 x 50 mg

Name of therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by strength/day of treatment	Treatment days/ Patient/ Year	Average annual consumption by strength
	30 mg/m² = 57 mg	57 mg	1 x 50 mg + 1 x 10 mg	34,8	34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with a third-generation cytostatic drug (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed (except in the case of predominantly squamous histology)) cf. Annex VI to Section K of the Pharmaceutical Directive					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
Docetaxel	75 mg/m² = 142.5 mg	142.5 mg	1 x 160 mg	17.4	17.4 x 160 mg
Gemcitabine	1250 mg/m² =2375 mg	2375 mg	1 x 2000 mg + 2 x 200 mg	34.8	34.8 x 2000 mg + 69.6 x 200 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17.4	17.4 x 150 mg + 34.8 x 100 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg
Vinorelbine	25 mg/m² = 47.5 mg	47.5 mg	1 x 50 mg	34.8	34.8 x 50 mg
	30 mg/m² = 57 mg	57 mg	1 x 50 mg + 1 x 10 mg	34.8	34.8 x 50 mg + 34.8 x 10 mg
Carboplatin in combination with nab-paclitaxel					
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg
Pembrolizumab in combination with pemetrexed and platinum-containing chemotherapy (only for patients with non-squamous histology)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Pemetrexed	500 mg/m² = 950 mg	950 mg	2 x 500 mg	17.4	34.8 x 500 mg

Name of therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by strength/day of treatment	Treatment days/ Patient/ Year	Average annual consumption by strength
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
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
Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel (only for patients with squamous histology)					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
Carboplatin	500 mg/m² = 950 mg	950 mg	1 x 600 mg + 2 x 150 mg + 1 x 50 mg	17.4	17.4 x 600 mg + 34.8 x 150 mg + 17.4 x 50 mg
Paclitaxel	175 mg/m² = 332.5 mg	332.5 mg	2 x 100 + 1 x 150 mg	17.4	17.4 x 150 mg + 34.8 x 100 mg
nab-paclitaxel	100 mg/m² = 190 mg	190 mg	2 x 100 mg	52.2	104.4 x 100 mg

Costs:

Cost of medicinal product:

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 Sections 130 and 130a 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. For the calculation of the annual treatment costs, the required number of packs by strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Name of therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate § 130a SGB V	Cost after deduction of statutory rebates
Medicinal product to be assessed					
Ipilimumab 50 mg	10 ml IFC	€3,849.07	€ 1.77	€ 216.54	€ 3,630.76
Nivolumab 40 mg	4 ml IFC	€ 544.32	€ 1.77	€ 29.53	€ 513.02

Name of therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate § 130a SGB V	Cost after deduction of statutory rebates
Nivolumab 100 mg	10 ml IFC	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Carboplatin 50 mg	5 ml INF	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 150 mg	15 ml INF	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	60 ml INF	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cisplatin 50 mg	50 ml IFC	€ 47.43	€ 1.77	€ 1.73	€ 43.93
Cisplatin 100 mg	100ml IFC	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Paclitaxel 100 mg	1 IFC	€ 303.80	€ 1.77	€ 13.89	€ 288.14
Paclitaxel 150 mg	1 IFC	€ 450.59	€ 1.77	€ 20.86	€ 427.96
Pemetrexed 500 mg	1 PIK	€ 2,533.30	€ 1.77	€ 379.41	€ 2,152.12
Appropriate comparator therapy					
Carboplatin 50 mg	5 ml INF	€ 34.38	€ 1.77	€ 1.11	€ 31.50
Carboplatin 150 mg	15 ml INF	€ 82.79	€ 1.77	€ 3.40	€ 77.62
Carboplatin 600 mg	60 ml INF	€ 300.57	€ 1.77	€ 13.74	€ 285.06
Cisplatin 10 mg	10 ml IFC	€ 17.26	€ 1.77	€ 0.30	€ 15.19
Cisplatin 50 mg	50 ml IFC	€ 47.43	€ 1.77	€ 1.73	€ 43.93
Cisplatin 100 mg	100ml IFC	€ 76.31	€ 1.77	€ 3.10	€ 71.44
Docetaxel 160 mg	8 ml IFC	€ 1,397.36	€ 1.77	€ 175.44	€ 1,220.15
Gemcitabine 200 mg	2 ml IFC	€ 28.57	€ 1.77	€ 0.83	€ 25.97
Gemcitabine 2000 mg	20 ml IFC	€ 193.96	€ 1.77	€ 8.68	€ 183.51
nab- Paclitaxel 100 mg	1 PIS	€ 429.09	€ 1.77	€ 52.91	€ 374.41
Paclitaxel 100 mg	1 IFC	€ 303.80	€ 1.77	€ 13.89	€ 288.14
Paclitaxel 150 mg	1 IFC	€ 450.59	€ 1.77	€ 20.86	€ 427.96
Pembrolizumab 100 mg	4 ml IFC	€ 3,037.06	€ 1.77	€ 170.17	€ 2,865.12
Pemetrexed 500 mg	1 PIK	€ 2,533.30	€ 1.77	€ 379.41	€ 2,152.12
Vinorelbine 10 mg	1 ml IFC	€ 41.39	€ 1.77	€ 3.84	€ 35.78
Vinorelbine 50 mg	5 ml IFC	€ 156.44	€ 1.77	€ 18.40	€ 136.27

Name of therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate § 130a SGB V	Cost after deduction of statutory rebates
Abbreviations: IFC = concentrate for the preparation of an infusion solution, INF = infusion solution, PIC = powder for the preparation of an infusion solution concentrate, PIS = powder for the preparation of an infusion suspension					

Last revised Lauer-Taxe: 15 May 2021

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 when using the drug to be evaluated and the appropriate comparator therapy according to the product information, the costs incurred for this are to be taken into account as costs for additionally required SHI services.

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

Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Annex I of 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 5aSGB V, when a non-prescription medicinal product is dispensed and invoiced in accordance with Section 300, a medicinal product dispensing price in the amount of the dispensing price of the pharmaceutical company plus the surcharges in accordance with Sections 2 and 3 of the Pharmaceutical Price Ordinance in the version valid on 31 December 2003 applies to the insured.

Name of therapy	Package 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
Medicinal product to be assessed							
Cisplatin							
Antiemetic treatment							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% Inf. Solution, 37.5 g/day	10 x 500 ml INF	€ 106.22	€ 5.31	€ 9.81	€ 91.10	2	€ 91.10
Sodium chloride 0.9% Inf. Solution,	6 x 1,000 ml INF	€ 24.26	€ 1.21	€ 1.98	€ 21.07	2	€21.07

Name of therapy	Package 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
3 l - 4.4 l/day	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58		€ 32.58
Paclitaxel							
Dexamethasone 20 mg[4]	10 TAB	€ 32.14	€ 1.77	€ 0.00	€ 30.37	2	€ 30.37
Dimetind i.v. 1 mg/10 kg	5 x 4 mg SFI	€ 18.62	€ 1.77	€ 1.92	€ 14.93	2	€ 14.93
Cimetidine 300 mg IV. [4]	10 IFC x 200 mg	€ 21.55	€ 1.77	€ 0.00	€ 19.78	2	€ 19.78
Pemetrexed							
Dexamethasone[4] 2 x 4 mg	20 TAB 4 mg	€ 24.34	€ 1.77	€ 1.05	€ 21.52	6	€ 21.52
Folic acid: 350 - 1,000 µg/day[5]	100 x 400 µg TAB	€ 16.21	€ 0.81	€ 2.38	€ 13.02	70	€ 13.02
	50 x 400 µg TAB	€ 8.89	€ 0.44	€ 1.14	€ 7.31		€ 20.33
Vitamin B12[4] 1.000 µg/day, every 3 cycles	5 x 1.000 µg SFI	€ 4.49	€ 0.22	€ 0.19	€ 4.08	1	€ 4.08
Appropriate comparator therapy							
Cisplatin							
In clinical practice, an appropriate antiemetic treatment is established before and/or after administration of cisplatin. The product information for cisplatin does not provide any specific information on this, which is why the necessary costs cannot be quantified.							
Mannitol 10% Inf. 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% Inf. Solution,	10 x 1,000 ml INF	€ 35.47	€ 1.77	€ 1.12	€ 32.58	17.4	€ 170.07 -

4fixed reimbursement rate

5 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.

Name of therapy	Package 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
3 - 4.4 l/day	10 x 500 ml INF	€ 22.72	€ 1.14	€ 0.69	€ 20.89		€ 263.11
Paclitaxel							
Dexamethasone 20 mg[4]	50 TAB	€ 118.61	€ 1.77	€ 0.00	€ 116.84	17.4	€ 81.32
Dimetind i.v. 1 mg/10 kg	5 x 4 mg SFI	€ 18.62	€ 1.77	€ 1.92	€ 14.93	17.4	€ 103.91
Cimetidine 300 mg IV. [4]	10 IFC x 200 mg	€ 21.55	€ 1.77	€ 0.00	€ 19.78	17.4	€ 68.83
Pemetrexed							
Dexamethasone[4] 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[5]	100 x 400 µg TAB	€ 16.21	€ 0.81	€ 2.38	€ 13.02	365	€47.52 - €95.05
Vitamin B12[4] 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: IFC = concentrate for the preparation of an infusion solution; SFI = solution for injection; INF = infusion solution; TAB = tablets							

Other SHI benefits:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe)(Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1.10.2009 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 containing cytostatics amount to a maximum of €81 per ready-to-use preparation, and for the production of parenteral solutions with monoclonal antibodies to a maximum of €71 per ready-to-use unit. These additional other costs do not add to the pharmacy sales price, but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (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 sales 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 special agreement on contractual unit costs retail pharmacist services (Hilfstaxe).

3. Bureaucratic cost 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 7 July 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. Working group 35a determined the appropriate comparator therapy at its session on 13 October 2020.

On 2 December 2020 the pharmaceutical company submitted a dossier for the benefit assessment of ipilimumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 17 November 2020 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 ipilimumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2021. The deadline for submitting written statements was 6 April 2021.

The oral hearing was held on 27 April 2021.

By letter dated 29 April 2021, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 20 May 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 assessment of the written statements received and the oral hearing were discussed at the session of the subcommittee on 25 May 2021, and the draft resolution was approved.

At its session on 3 June 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 July 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	13 October 2020	Implementation of the appropriate comparator therapy
Working group Section 35a	13 April 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal product	27 April 2021 29 April 2021	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	4 May 2021 18 May 2021	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	25 May 2021	Final discussion of the draft resolution
Plenum	3 June 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 June 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The chairman

Prof. Hecken