Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Pembrolizumab (new therapeutic indication: non-small cell lung carcinoma, high risk of recurrence, neoadjuvant and adjuvant treatment, monotherapy or combination with platinum-based chemotherapy)

of 17 October 2024

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 all 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 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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

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

On 25 March 2024, pembrolizumab 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 from 12.12.2008, sentence 7).

On 19 April 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.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 pembrolizumab with the new therapeutic indication

"in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 August 2024 on the G-BA website (www.g-ba.de), 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 pembrolizumab 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, 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 pembrolizumab.

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 Pembrolizumab (Keytruda) in accordance with the product information

KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults.

Therapeutic indication of the resolution (resolution of 17.10.2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

Appropriate comparator therapy for pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant treatment followed by pembrolizumab as monotherapy for adjuvant treatment:

Neoadjuvant treatment:

Nivolumab in combination with a platinum-based therapy

Followed by adjuvant treatment:

best supportive care

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

Appropriate comparator therapy for pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant treatment followed by pembrolizumab as monotherapy for adjuvant treatment:

Patient-individual therapy with selection of:

- preoperative (neoadjuvant) systemic chemotherapy with selection of
  - cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)
    and
  - carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) and
- simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy,

taking into account the tumour stage, the tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin.

Followed by adjuvant treatment:

best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

on 1. In addition to pembrolizumab, the active ingredient nivolumab is approved for neoadjuvant treatment in this therapeutic indication.

In addition to pembrolizumab, the active ingredients atezolizumab and vinorelbine are approved for adjuvant treatment.

on 2. In the present therapeutic indication, a preoperative (neoadjuvant) radiotherapy is considered as non-medicinal treatment.

Preoperative (neoadjuvant) radiotherapy and post-operative (adjuvant) radiotherapy (stage III) are generally considered as non-medicinal treatment in this therapeutic indication.

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

Neoadjuvant treatment:

- Nivolumab: resolution of 1 February 2024

Adjuvant treatment:

- Atezolizumab: resolution of 05.01.2023

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. No written feedback was received.

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 care.

The evidence for the perioperative treatment setting in this therapeutic indication, neoadjuvant treatment followed by adjuvant treatment, is limited.

Patients at high risk of recurrence with resectable NSCLC in tumour stages II, IIIA and IIIB (N2) were enrolled in this therapeutic indication.

The recommendations in guidelines on neoadjuvant therapy options are made, depending on the respective tumour stage. For the early tumour stages (stages IIA and IIB), which are covered by this therapeutic indication, the recommendations regarding neoadjuvant chemotherapy are inconsistent and the evidence for neoadjuvant therapy is limited overall. There are also indications that in the early tumour stages, adjuvant chemotherapy is given a higher priority overall than neoadjuvant chemotherapy, if (neo)adjuvant chemotherapy is indicated. The appropriate comparator therapy was determined in the present therapeutic indication on the condition that the decision was made in favour of neoadjuvant therapy.

a) <u>Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment</u>

The S3 guideline recommends neoadjuvant, combined immunochemotherapy in tumour stages II and IIIA3/IIIB (T3N2 only) for patients with resectable tumours and PD-L1 expression ≥ 1%. The S3 guideline states that nivolumab in combination with platinum-based chemotherapy from the label-enabling Checkmate 816 study is an approved therapy option for patients with tumour cell PD-L1 expression ≥ 1% in the neoadjuvant treatment setting.

The scientific-medical societies, represented by the Working Group for Internal Oncology of the German Cancer Society (AIO), the German Society for Haematology and Medical Oncology (DGHO) and the German Respiratory Society (hereinafter: scientific-medical societies) explain in a joint written statement in the written statement procedure that there are several appropriate comparator therapies for

resectable NSCLC. The significance of neoadjuvant, systemic therapy is currently changing. Platinum-based chemotherapy alone had a favourable effect on various disease-related factors, but would not have significantly prolonged progression-free and overall survival period. Neoadjuvant therapy with immune checkpoint inhibitors would have the advantage that broad T-cell stimulation by the tumour can take place at the time of treatment. On the contrary, there were weaknesses in the underlying approval study for nivolumab. Furthermore, the formation of sub-populations based on PD-L1 expression is controversial. Currently, neoadjuvant therapy is recommended as a combination of immune checkpoint inhibitors with platinum-based therapy - this was confirmed in the oral hearing.

Nivolumab in combination with platinum-based chemotherapy is approved for the neoadjuvant treatment of adults with resectable non-small cell lung carcinoma at high risk of recurrence with tumour cell PD-L1 expression ≥ 1%. By resolution of 1 February 2024, a hint for a non-quantifiable additional benefit was identified in the benefit assessment of this combination of active ingredients.

Against this background, the G-BA determined nivolumab in combination with a platinum-based therapy as an appropriate comparator therapy for neoadjuvant treatment of patient population a) with a tumour cell PD-L1 expression ≥ 1%.

For the subsequent adjuvant treatment or for the postoperative phase, best supportive care is determined as an appropriate comparator therapy.

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

In addition, the guidelines for neoadjuvant treatment of resectable NSCLC refer to systemic neoadjuvant chemotherapy for patients who do not have tumour cell PD-L1 expression ≥ 1%. However, there are hardly any specific recommendations in the guidelines with regard to the active ingredients used in chemotherapy. In the procedure for neoadjuvant therapy with nivolumab in combination with platinum-based chemotherapy (resolution of 01.02.2024), platinum-based combination chemotherapy was presented as the standard in the written statement of the AKdÄ and in the joint written statement of four scientific-medical societies on the question of comparator therapy.

The selection of active ingredients depends on patient-individual criteria, in particular with regard to existing comorbidities and tumour histology. In the nivolumab procedure, the scientific-medical societies state that platinum-based combination chemotherapy is carried out with a platinum derivative in combination with a third-generation cytostatic. However, there is no single chemotherapy standard. The platinum derivatives cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine or pemetrexed were mentioned as effective combinations.

Carboplatin has a different side effect profile compared to cisplatin. In view of the essential therapeutic objective of taking patients to surgery following neoadjuvant therapy in order to perform a tumour resection, the side effect profile of cisplatin may give rise to potential risks depending on existing comorbidities and general condition, which may affect the feasibility of the planned surgery. These facts were presented in the joint statement of the scientific-medical societies on the benefit assessment of nivolumab and it was stated in this regard that carboplatin is therefore also regularly used in treatment.

In the context of patient-individual treatment decision, carboplatin is the platinum derivative of choice in the case of contraindications to cisplatin. On the contrary, carboplatin is preferred over cisplatin depending on existing comorbidities and the patient's general condition, if there are potential risks due to the side effect profile of cisplatin with regard to the feasibility of the surgery.

Depending on the tumour stage, simultaneous radiochemotherapy is a further standard in the preoperative treatment setting. According to the guidelines, chemotherapy for simultaneous radiochemotherapy is based on platinum-based (cisplatin or carboplatin) combination chemotherapy. No sufficiently clear standard can be established for the other components of chemotherapy in addition to cisplatin or carboplatin.

Against this background, the appropriate comparator therapy for the patient population b) with a PD-L1 expression < 1% was a patient-individual therapy with a choice of preoperative (neoadjuvant) systemic chemotherapy (with a choice of either cisplatin or carboplatin, in each case in combination with a third-generation cytostatic) and simultaneous radiochemotherapy (with platinum-based (cisplatin or carboplatin) combination chemotherapy), taking into account the tumour stage, tumour histology, the presence of a Pancoast tumour and the feasibility of an R0 resection, as well as the prerequisites for the use of carboplatin.

For the subsequent adjuvant treatment or for the postoperative phase, best supportive care is determined as an appropriate comparator therapy.

For the implementation of patient-individual therapy in a direct comparator study, it is expected that the study doctor will have a choice of several treatment options that will allow a patient-individual treatment decision to be made, taking into account the criteria mentioned (multi-comparator study). The selection and, if necessary, limitation of treatment options must be justified. The patient-individual treatment decision with regard to the comparator therapy should be made before group allocation (e.g. randomisation). If only a single comparator study is presented, the extent to which conclusions can be drawn about a sub-population will be examined as part of the benefit assessment.

The above-mentioned active ingredients or combinations of active ingredients - cisplatin and carboplatin, each in combination with a third-generation cytostatic - are not approved for the neoadjuvant therapy of resectable NSCLC. Besides the medicinal product to be assessed here, no other approved medicinal products are available overall for patients with tumour cell PD-L1 expression < 1% (patient population b) in this therapeutic indication.

The use of cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine or pemetrexed is medically necessary for the neoadjuvant treatment of patients with NSCLC with tumour cell PD-L1 expression < 1%.

On the basis of evidence-based guideline recommendations[2,3], the statement of the scientific-medical societies in the present benefit assessment procedure and the statements of the scientific-medical societies as well as the written statement of the

[2] Oncology guideline programme (German Cancer Society (DKG), German Cancer Aid (DKH), Association of the Scientific-Medical Societies in Germany (AWMF)). Prevention, diagnosis, therapy and after-care of lung cancer, guideline report 3.0 [online]. AWMF registry number 020-007OL. Berlin (GER): Oncology guideline programme; 2024.

[3] Singh et al. Management of Stage III Non–Small-Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update. J Clin Oncol 2023; 41:4430-4432.

AkdÄ on the question of comparator therapy in the benefit assessment procedure of nivolumab (resolution of 01.02.2024), the off-label use according to the generally recognised state of medical knowledge in the therapeutic indication to be assessed is considered the therapy standard. With the medicinal product to be assessed, a medicinal product approved for the sub-population of patients with tumour cell PD-L1 expression < 1% in the therapeutic indication will be available for the first time (Section 6, paragraph 2, sentence 3, number 1 AM-NutzenV).

The determination of the off-label use of medicinal products as an appropriate comparator therapy by resolution on the benefit assessment according to Section 35a paragraph 3 SGB V does not affect the procedure according to Section 35c SGB V.

According to the S3 guideline, tumour cell PD-L1 expression is a decision criterion for anti-neoplastic induction therapy. The G-BA therefore considers it appropriate to divide the patients in the therapeutic indication into patient population a) and patient population b), depending on the tumour cell PD-L1 expression and analogous to the marketing authorisation characteristic of tumour cell PD-L1 expression ≥ 1% of neoadjuvant immunochemotherapy.

Best Supportive Care (BSC) is understood as the therapy that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life. The guidelines recommend collection and treatment of post-therapeutic complications that may occur after surgery or radiotherapy.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of pembrolizumab is assessed as follows:

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

An additional benefit is not proven.

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

An additional benefit is not proven.

Justification:

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

and

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

The pharmaceutical company presented the results of the KEYNOTE 671 study to demonstrate an additional benefit of pembrolizumab for neoadjuvant treatment followed by adjuvant treatment of resectable non-small cell lung carcinoma at high risk of recurrence. The patients initially received neoadjuvant treatment as the treatment regimen. Surgery was performed within 4 to 8 weeks after the last neoadjuvant dose. The patients then received adjuvant treatment within 4 to 12 weeks of the R0 resection.

KEYNOTE 671 is an ongoing, double-blind, randomised, multicentre study comparing pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) followed by pembrolizumab as monotherapy (adjuvant) on the one hand with platinum-based chemotherapy (neoadjuvant) followed by placebo (adjuvant) on the other.

A total of 797 previously untreated adults with histologically confirmed and resectable stage II, IIIA and IIIB (T3-4N2 only) NSCLC (each according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging criteria) were enrolled in the study. 397 patients were assigned to the intervention arm and 400 patients to the control arm.

The treatment options (neoadjuvant treatment) as part of platinum-based chemotherapy in both arms are cisplatin + gemcitabine (for squamous cell carcinoma) or cisplatin + pemetrexed (for non-squamous cell carcinoma). Furthermore, patients who have undergone surgery can receive radiotherapy within 4 to 8 weeks of the surgery, if necessary (positive margins of the resectate, extracapsular tumour growth of the lymph nodes or severe residual disease).

The use of other medicinal products is generally permitted in the adjuvant treatment phase.

The pharmaceutical company presented the data for the total population (no subdivision according to tumour cell PD-L1 expression) in the dossier. Of the patients enrolled, 289 (36%) had tumour cell PD-L1 expression < 1% and 508 (64%) had tumour cell PD-L1 expression ≥ 1%.

The study ongoing since April 2018 is being conducted in 227 study sites in Asia, Australia, Europe, South Africa as well as North America and South America.

Data cut-offs from 29 July 2022 and 10 July 2023 are available for the KEYNOTE 671 study.

Limitations of the study

On the percentage of patients without surgery/ without R0 resection

According to the information on the post-hoc-adapted EFS provided by the pharmaceutical company's statement, the percentage of subjects who did not have surgery in the relevant sub-population was 12.3% in the intervention arm and 7.9% in the control arm. The percentage of patients in whom local progression prevented the planned surgery was 0% in the intervention arm and 0.7% in the comparator arm. Radiological disease progression according to RECIST 1.1, which prevented the planned surgery, occurred in 4.3% of subjects in the intervention arm and in 4.0% of subjects in the control arm. The percentage of unsuccessful surgeries (no R0 resection) was 5.1% in the intervention arm and 10.6% in the control arm. Against the background of the present therapeutic indication, which is based on resectable non-small cell lung carcinoma, these rates appear relatively high overall and can therefore only conditionally be transferred to the German healthcare context. In this regard, it was noted in the oral hearing of the clinical experts that the rate of subjects receiving surgery after neoadjuvant chemoimmunotherapy is significantly higher in clinical practice.

<u>Implementation of the appropriate comparator therapy</u>

To demonstrate an additional benefit, the pharmaceutical company considered a summarised patient population in the dossier for the benefit assessment and presented the KEYNOTE 671

study. The pharmaceutical company chose neoadjuvant therapy with cisplatin + gemcitabine (for squamous cell carcinoma) or cisplatin + pemetrexed (for non-squamous cell carcinoma) as a comparison. In Module 3A of the dossier, they refer to the patient-individual therapy previously, which was determined during the consultation and related to the entire patient population in the present therapeutic indication.

In determining the appropriate comparator therapy for the present procedure, the G-BA differentiated according to the characteristic of tumour cell PD-L1 expression. The present assessment was conducted for patients with resectable non-small cell lung carcinoma at high risk of recurrence and with tumour cell PD-L1 expression ≥ 1% (patient group a) and tumour cell PD-L1 expression < 1% (patient group b) compared with the respective appropriate comparator therapy determined by the G-BA.

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

For adults with PD-L1 expression ≥ 1% for neoadjuvant, and then continued as adjuvant treatment of resectable non-small cell lung carcinoma at high risk of recurrence, no suitable data are available for assessment of the additional benefit. The KEYNOTE 671 study is unsuitable for assessment of the additional benefit because the appropriate comparator therapy "nivolumab in combination with a platinum-based therapy" determined by the G-BA for the present resolution for patient population a) in the neoadjuvant treatment phase has not been implemented. Thus, an additional benefit compared to the appropriate comparator therapy is not proven.

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

As part of the written statement procedure, the pharmaceutical company subsequently submitted results from the KEYNOTE 671 study for the sub-population with tumour cell PD-L1 expression < 1% (patient population b). 138 patients from the relevant sub-population were enrolled in the intervention arm of the KEYNOTE 671 study and 151 patients in the comparator arm.

For patients with a tumour cell PD-L1 expression < 1%, the G-BA determined the appropriate comparator therapy to be a patient-individual therapy in neoadjuvant treatment with a choice of systemic chemotherapy (either cisplatin or carboplatin, each in combination with a third-generation cytostatic) or simultaneous radiochemotherapy.

Depending on the histology of the NSCLC, the principal investigators could choose between the treatment options cisplatin in combination with gemcitabine (for squamous cell histology) and cisplatin in combination with pemetrexed (for non-squamous cell histology).

For the selection of therapy options as part of patient-individual therapy

It would have been desirable if the principal investigators had been able to choose from further treatment options as part of the patient-individual therapy. In particular, the use of taxanes, which represent a preferred standard in the German healthcare context according to the clinical experts in the oral hearing, would have been recommendable. With regard to the platinum component, a choice between cisplatin and oxaliplatin would be desirable due to the different side effect profile. Simultaneous radiochemotherapy in the neoadjuvant treatment phase was not permitted in the KEYNOTE 671 study. However, patients for whom simultaneous radiochemotherapy would have been indicated in the neoadjuvant treatment

phase (patients with Pancoast tumours) are included according to the present therapeutic indication.

Overall, the patient-individual therapy for the neoadjuvant treatment phase is considered to be implemented for patient group b) with a tumour cell PD-L1 expression < 1%. With reference to this sub-population, the comparator therapy of the KEYNOTE 671 study thus corresponds to an adequate implementation of the appropriate comparator therapy in the present case despite the uncertainties described.

On the subgroup analyses

The pharmaceutical company did not present any subgroup analyses for the sub-population with tumour cell PD-L1 expression of < 1% in the evaluations submitted in the written statement procedure. No statements about potential effect modifications are possible due to the absence of subgroup analyses.

Mortality

Overall survival was defined in the KEYNOTE 671 study as the time between randomisation and death, regardless of the underlying cause of death.

There was no statistically significant difference for pembrolizumab in combination with cisplatin and gemcitabine or cisplatin and pemetrexed (neoadjuvant treatment) followed by pembrolizumab (adjuvant treatment) compared to cisplatin and gemcitabine or cisplatin and pemetrexed (neoadjuvant treatment) followed by placebo (adjuvant treatment).

Based on the information for the total study population on the subsequent therapies used after the end of the study medication, it is particularly striking that relatively few patients with distant metastases in the comparator arm received subsequent therapy with an immune checkpoint inhibitor, which represents the current therapy standard. Relevant information on subsequent therapies, such as data on the percentage of patients with distant metastases, was not provided to the full extent for the relevant sub-population. Overall, there is uncertainty with regard to the subsequent therapies used.

Morbidity

Failure of the curative approach (event-free survival, EFS)

Patients in the present therapeutic indication are treated with a curative therapeutic approach. The failure of a curative therapeutic approach is fundamentally patient-relevant.

The significance of the EFS endpoint depends on the extent to which the selected individual components are suitable for adequately reflecting the failure of potential cure by the present curative therapeutic approach.

The EFS endpoint was defined in the statistical analysis plan (SAP) of the KEYNOTE 671 study as the time from randomisation to the occurrence of one of the following events:

- radiological disease progression according to RECIST 1.1 (for patients who have not undergone or will not undergo surgery or who have severe residual disease after incomplete resection [R2 resection]),
- local progression (primary tumour or regional lymph nodes) that prevents the planned surgery,

- unresectable tumour,
- local recurrence or distant recurrence (for patients who are disease-free after surgery [R0 resection] or patients with microscopically positive margins [R1 resection]) or
- death from any cause.

In addition, the pharmaceutical company presented another operationalisation of the EFS endpoint as "Post-hoc-adapted event-free survival". This was operationalised as the time from randomisation to the first occurrence of one of the following events:

- radiological disease progression according to RECIST 1.1 that prevents the planned surgery
- local progression (primary tumour or regional lymph nodes) that prevents the planned surgery
- no surgery (for patients who switched to the adjuvant phase without surgery)
- unresectable tumour
- not disease-free after surgery (patients with R1 or R2 resection)
- local recurrence or distant recurrence (for patients who are disease-free after surgery [R0 resection])
- death from any cause

The presented operationalisation "Post-hoc-adapted event-free survival" differs from the pre-specified operationalisation primarily in that the failure to achieve an R0 resection (patients who are not disease-free after surgery and have an R1 or R2 resection) is also counted as an event. In addition, the absence of surgery - switching to the adjuvant phase without surgery - is counted as an event.

It is unclear how the event "Local progression (primary tumour or regional lymph nodes) that prevents the planned surgery" differs from the event "Radiological disease progression according to RECIST 1.1" and whether the former is also determined radiologically. This uncertainty has no consequence since the event "Local progression (primary tumour or regional lymph nodes) that prevents the planned surgery" only occurred once.

Overall, the operationalisation presented post hoc "Post-hoc-adapted event-free survival" comprehensively reflects the failure of the curative therapeutic approach compared to the pre-specified operationalisation and is used for the present benefit assessment. For the assessment, the percentage of patients with an event (event rate) as well as the time-dependent evaluations (EFS) are considered.

There were no statistically significant differences between the treatment arms in each case.

Symptomatology (assessed using EORTC QLQ-C30 and EORTC QLQ-LC13) and health status (assessed using EQ-5D VAS)

The symptomatology of the patients is assessed in the KEYNOTE 671 study with the EORTC QLQ-C30 and the disease-specific additional module EORTC QLQ-LC13. The health status is assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

With their statement, the pharmaceutical company submitted continuous evaluations using a mixed model for repeated measures (MMRM) for the EORTC QLQ-C30, the EORTC QLQ-LC13 and the EQ-5D VAS.

The data presented on the Patient Reported Outcomes (PROs) are not used for the assessment, as the return rates are strongly decreasing and differential in the course of the observation. Irrespective of this, the data presented cannot generally be interpreted meaningfully due to the long and varying survey-free periods between the neoadjuvant and adjuvant treatment phases (at least 8 weeks, but also up to 20 weeks in the patient-individual case). Overall, the results are therefore not usable for the present benefit assessment.

Quality of life

Patients' quality of life is assessed in the KEYNOTE 671 study using the EORTC QLQ-C30.

With their statement, the pharmaceutical company submitted continuous evaluations using a mixed model for repeated measures (MMRM) for the EORTC QLQ-C30.

The data presented on the Patient Reported Outcomes (PROs) are not used for the assessment, as the return rates are strongly decreasing and differential in the course of the observation. Irrespective of this, the data presented cannot generally be interpreted meaningfully due to the long and varying survey-free periods between the neoadjuvant and adjuvant treatment phases (at least 8 weeks, but also up to 20 weeks in the patient-individual case). Overall, the results are therefore not usable for the present benefit assessment.

Side effects

Adverse events in total

Adverse events occurred in almost all patients. The results for the endpoint "total adverse events" are only presented additionally.

Serious AEs (SAEs), severe AEs (CTCAE grade ≥ 3), therapy discontinuation due to AEs

There were no statistically significant differences between the treatment arms for the endpoints of SAEs, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs.

Specific AEs

Immune-mediated SAE, peripheral oedema (AE), general disorders and administration site conditions (SAE)

In Module 4 A of the dossier, the pharmaceutical company presented evaluations for SAEs and severe AEs for the total population under the term of immune-mediated adverse events. According to the information provided by the pharmaceutical company, these endpoints were collected using a predefined PT list. As part of the written statement procedure, results for patients with a tumour cell PD-L1 expression < 1% were presented for serious and severe events of special interest, without describing these in more detail. It is assumed that the subsequently submitted documents are the endpoints defined in Module 4 A of the dossier. For the endpoints of immune-mediated SAEs, peripheral oedema (AEs), and general disorders and administration site conditions (SAEs), there was a disadvantage of the intervention arm compared to the control arm.

The overall assessment of the results on side effects showed neither an advantage nor a disadvantage of pembrolizumab in combination with cisplatin and gemcitabine or cisplatin and pemetrexed (neoadjuvant treatment) followed by pembrolizumab (adjuvant treatment). In detail, there are disadvantages in the specific AEs.

Overall assessment

For the benefit assessment of pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant treatment) followed by pembrolizumab (adjuvant treatment), data are available from the double-blind, randomised KEYNOTE 671 study on mortality, morbidity, quality of life and side effects compared with cisplatin and gemcitabine or cisplatin and pemetrexed (neoadjuvant treatment) followed by placebo (adjuvant treatment). Overall, the selected patient-individual therapy for the neoadjuvant treatment phase followed by placebo in the adjuvant treatment phase is considered to be an adequate implementation of the appropriate comparator therapy in the present case, despite the uncertainties described.

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups. Uncertainties remain regarding the subsequent therapies given after completion of the study medication.

In the endpoint category of morbidity, there was no statistically significant difference between the treatment arms for the endpoint "Failure of the curative therapeutic approach". No assessable data are available on symptomatology (assessed using EORTC QLQ-C30 and EORTC QLQ-LC13) and health status (assessed using EQ-5D VAS).

Likewise, no assessable data are available on health-related quality of life.

There was no statistically significant difference between the treatment arms regarding side effects. In detail, there are disadvantages in the specific AEs.

In the overall analysis, there were no differences between the treatment arms for any of the endpoint categories of mortality, morbidity, health-related quality of life and side effects. An additional benefit of pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant treatment) followed by pembrolizumab (adjuvant treatment) compared with cisplatin and gemcitabine or cisplatin and pemetrexed (neoadjuvant treatment) followed by placebo (adjuvant treatment) is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab. The therapeutic indication assessed here is as follows:

"KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults."

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

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

   and

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

The present assessment is conducted separately for patient groups a) and b) against the respective appropriate comparator therapies determined by the G-BA.

Patient group a)

Nivolumab in combination with a platinum-based therapy was determined as the appropriate comparator therapy for neoadjuvant treatment, and best supportive care for adjuvant treatment.

For adults with PD-L1 expression ≥ 1% for neoadjuvant, and then continued as adjuvant treatment of resectable non-small cell lung carcinoma at high risk of recurrence, no suitable data are available for assessment of the additional benefit. The KEYNOTE 671 study is unsuitable for assessment of the additional benefit because the appropriate comparator therapy "nivolumab in combination with a platinum-based therapy" determined by the G-BA for the present resolution for patient population a) in the neoadjuvant treatment phase has not been implemented. Thus, an additional benefit compared to the appropriate comparator therapy is not proven.

Patient group b)

As an appropriate comparator therapy, the G-BA determined a patient-individual therapy with a choice of different platinum-based chemotherapies and the option of simultaneous radiochemotherapy for the neoadjuvant treatment. Best supportive care was determined for the subsequent adjuvant treatment.

In the KEYNOTE 671 study, pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) was compared with cisplatin and gemcitabine or cisplatin and pemetrexed (neoadjuvant) followed by placebo (adjuvant).

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups. Uncertainties remain regarding the subsequent therapies used after completion of the study medication.

In the endpoint category of morbidity, there was no statistically significant difference between the treatment arms for the endpoint "Failure of the curative therapeutic approach". No assessable data are available on symptomatology (assessed using EORTC QLQ-C30 and EORTC QLQ-LC13) and health status (assessed using EQ-5D VAS).

There was no statistically significant difference between the treatment arms regarding side effects. In detail, there are disadvantages in the specific AEs.

In the overall analysis, there was no additional benefit of pembrolizumab in combination with platinum-based chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared with the appropriate comparator therapy.

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 resolution is based on the information from the dossier of the pharmaceutical company for the total population. With their statement, the pharmaceutical company subsequently

submitted percentage values for the sub-population with a tumour cell PD-L1 expression of < 1% (patient population b). The G-BA based its resolution on the percentage values of 63.7% for patients with tumour cell PD-L1 expression of ≥ 1% and of 36.3% for patients with PD-L1 expression <1% as the best approximation from the IQWiG's Addendum (G24-23).

The derivation of the patient numbers from the pharmaceutical company's dossier is basically comprehensible, but is also subject to uncertainties that lead to an underestimation. Uncertainties exist regarding the exclusion of patients with Pancoast tumours and in particular the restriction to patients who have received neoadjuvant therapy in the past. Due to the last described restriction of the pharmaceutical company, patients who have not received neoadjuvant therapy but would be eligible for it according to the marketing authorisation are not considered. According to IQWiG's estimate (Addendum G24-23), these limitations in the derivation of the patient numbers are inappropriate or should be considered too severe a restriction. The patient numbers are presented without the steps criticised by IQWiG.

To derive the patient numbers, the incidence of lung carcinoma (diagnosis code C34.- according to ICD-10) forecast by the pharmaceutical company for 2024 (60,076 patients) is used as the basis for the calculations.

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

1. The percentage of patients with NSCLC is 73.6% to 83.6% (44,216 to 50,224 patients).
2. The percentage of patients in stages IIA to IIIB is 1.87% for IIA; 6.88% for IIB; 11.31% for IIIA and 8.32% for IIIB (12,548 to 14,253 patients).
3. The percentage of patients with anatomical lung resection is 69.35% for IIA, 66.98% for IIB, 49.12% for IIIA and 19.68% for IIIB (5,791 to 6,578 patients).
4. The percentage of adults with tumour cell PD-L1 expression ≥ 1% (patient population a) is 63.7% (3,689 to 4,190 patients).
5. The percentage of adults with tumour cell PD-L1 expression < 1% (patient population b) is 36.3% (2,102 to 2,388 patients).
6. The percentage of patients in the SHI target population is 87.8%.

   6a. Patient group a) (≥ 1%): (3,239 to 3,679 patients)
   6b. Patient group b) (< 1%): (1,846 to 2,097 patients)

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 Keytruda (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 8 October 2024):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology and oncology who are experienced in the treatment of patients with non-small cell lung carcinoma, as well as specialists in internal medicine and

pulmonology or specialists in pulmonary medicine and other doctors from specialist groups participating in the Oncology Agreement.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, instructions on the management of immune-mediated side effects potentially occurring with pembrolizumab as well as on infusion-related reactions.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 September 2024).

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

and

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

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 combination therapies presented for pembrolizumab in combination with platinum-based chemotherapy for neoadjuvant, and then as monotherapy for adjuvant treatment correspond to the treatment regimens used in the KEYNOTE 671 approval study.

For nivolumab in combination with platinum-based chemotherapy (patient population a); neoadjuvant phase), the treatment regimens used in the CheckMate 816 approval study are used. The respective dosage is based on the requirements in the product information.

Outpatient treatment is assumed with regard to the costs of radiotherapy as part of simultaneous radiochemotherapy.

As explained in Section 2.1.2 "Appropriate comparator therapy" under 4, the chemotherapy for simultaneous radiochemotherapy is based on platinum-based combination chemotherapy according to the information in the guidelines. No sufficiently clear standard can be established for the other components of chemotherapy in addition to cisplatin or carboplatin. For this reason, the costs of chemotherapy in the context of simultaneous radiochemotherapy cannot be quantified.

There are no approved medicinal products in this therapeutic indication for the therapy options determined as appropriate comparator therapy for patient population b) (neoadjuvant treatment) as part of patient-individual therapy. The cost representation of the individual therapy options is based on the respective referenced sources.

For the carboplatin + vinorelbine combination which was defined as the appropriate comparator therapy, no study could be identified that would allow cost representation. The costs can therefore not be quantified.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy for the

adjuvant treatment in both patient groups, best supportive care is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements of the official representative statistics "Microcensus 2021 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77.7 kg). This results in a body surface area of 1.91 m² (calculated according to Du Bois 1916).[4]

The dosage according to the target AUC of carboplatin is calculated using the Calvert formula and the estimation of renal function with the Cockcroft-Gault equation using the average height (women: 166 cm, men: 179 cm), the average weight (women 69.2 kg, men 85.8 kg) and the average age of women and men in Germany in 2021 (women: 46 years, men: 43.4 years) [5] and the mean standard serum creatinine concentration (women: 0.75 mg/dl, men: 0.9 mg/dl).[6]

The mean value formed from these doses for women (AUC 5 = 637 mg, AUC 5.5 = 700.7 mg, AUC 6 = 764.3 mg) and men (AUC 5 = 764.5 mg, AUC 5.5 = 841 mg, AUC 6 = 917.4 mg) (AUC 5 = 700.7 mg, AUC 5.5 = 771 mg, AUC 6 = 840.9 mg) was used as the basis for calculating the cost of carboplatin.

Radiotherapy

For radiotherapy, the S3 guideline is based on a total dose of 45 Gy with single doses of 1.8 Gy (once a day) or 1.5 Gy (twice a day). This results in 15 to 25 treatment days.

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:				
Patient populations a) and b)				
Neoadjuvant treatment: Pembrolizumab + platinum-based chemotherapy				
Pembrolizumab + cisplatin + pemetrexed				
Pembrolizumab	every 21 days or every 42 days	4 2	1 1	4 2

[4] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

[5] Federal Institute for Population Research, Average age of the population in Germany (1871-2021) https://www.bib.bund.de/DE/Fakten/Fakt/B19-Durchschnittsalter-Bevoelkerung-ab-1871.html

[6] DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 10 September 2024

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	on day 1 of a 21-day cycle	4	1	4
Pemetrexed[7]	on day 1 of a 21-day cycle	4	1	4
Pembrolizumab + cisplatin + gemcitabine				
Pembrolizumab	every 21 days or every 42 days	4 2	1 1	4 2
Cisplatin	on day 1 of a 21-day cycle	4	1	4
Gemcitabine[8]	on day 1 and 8 of a 21-day cycle	4	2	8
Adjuvant treatment: Pembrolizumab (monotherapy)				
Pembrolizumab	every 21 days or every 42 days	13 7	1 1	13 7
Best supportive care	Different from patient to patient			
Appropriate comparator therapy:				
Patient population a)				
Neoadjuvant treatment: Nivolumab + platinum-based chemotherapy				
Nivolumab + carboplatin + paclitaxel				
Nivolumab	1 x per 21-day cycle	3	1	3
Carboplatin	1 x per 21-day cycle	3	1	3
Paclitaxel	1 x per 21-day cycle	3	1	3
Nivolumab + cisplatin + pemetrexed				

[7] Only for patients with non-squamous cell histology
[8] Only for patients with a squamous epithelial histology

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Nivolumab	1 x per 21-day cycle	3	1	3
Cisplatin	1 x per 21-day cycle	3	1	3
Pemetrexed	1 x per 21-day cycle	3	1	3
Nivolumab + cisplatin + gemcitabine				
Nivolumab	1 x per 21-day cycle	3	1	3
Cisplatin	1 x per 21-day cycle	3	1	3
Gemcitabine	2 x per 21-day cycle	3	2	6
Adjuvant treatment: Best supportive care				
Best supportive care	Different from patient to patient			
Patient population b)				
Neoadjuvant treatment: Patient-individual therapy with selection of preoperative (neoadjuvant) systemic chemotherapy with selection of				
cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)				
Cisplatin + vinorelbine[9]				
Cisplatin	1 x per 21-day cycle	3	1	3
Vinorelbine	2 x per 21-day cycle	3	2	6
Cisplatin + paclitaxel[10]				
Cisplatin	1 x per 21-day cycle	2	1	2

[9] NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet. 2014 May 3;383(9928):1561-71. doi: 10.1016/S0140-6736(13)62159-5. Epub 2014 Feb 25

[10] Choi IS, Oh DY, Kwon JH, Kim SI, Park SR, Bak JY, Kim JH, Kim DW, Kim YT, Kim TY, You CK, Kim YW, Heo DS, Bang YJ, Sung SW, Park CI, Kim NK. Paclitaxel/Platinum-based perioperative chemotherapy and surgery in stage IIIA non-small cell lung cancer. Jpn J Clin Oncol. 2005 Jan;35(1):6-12. doi: 10.1093/jjco/hyi008

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Paclitaxel	1 x per 21-day cycle	2	1	2
Cisplatin + gemcitabine[9]				
Cisplatin	1 x per 21-day cycle	3	1	3
Gemcitabine	2 x per 21-day cycle	3	2	6
Cisplatin + docetaxel[11]				
Cisplatin	1 x per 21-day cycle	3	1	3
Docetaxel	1 x per 21-day cycle	3	1	3
Cisplatin + pemetrexed[12]				
Cisplatin	1 x per 21-day cycle	3	1	3
Pemetrexed	1 x per 21-day cycle	3	1	3
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)				
Carboplatin + vinorelbine				
No specification possible				
Carboplatin + paclitaxel[9]				
Carboplatin	1 x per 21-day cycle	3	1	3
Paclitaxel	1 x per 21-day cycle	3	1	3
Carboplatin + gemcitabine[13]				

[11] Cascone T, Gold KA, Swisher SG, Liu DD, Fossella FV, Sepesi B, Pataer A, Weissferdt A, Kalhor N, Vaporciyan AA, Hofstetter WL, Wistuba II, Heymach JV, Kim ES, William WN Jr. Induction Cisplatin Docetaxel Followed by Surgery and Erlotinib in Non-Small Cell Lung Cancer. Ann Thorac Surg. 2018 Feb;105(2):418-424. doi: 10.1016/j.athoracsur.2017.08.052

[12] Dy GK, Bogner PN, Tan W, Demmy TL, Farooq A, Chen H, Yendamuri SS, Nwogu CE, Bushunow PW, Gannon J, Adjei AA, Adjei AA, Ramnath N. Phase II study of perioperative chemotherapy with cisplatin and pemetrexed in non-small-cell lung cancer. J Thorac Oncol. 2014 Feb;9(2):222-30. doi: 10.1097/JTO.0000000000000062

[13] Detterbeck FC, Socinski MA, Gralla RJ, Edelman MJ, Jahan TM, Loesch DM, Limentani SA, Govindan R, Zaman MB, Ye Z, Monberg MJ, Obasaju CK. Neoadjuvant chemotherapy with gemcitabine-containing regimens in

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Carboplatin	1 x per 21-day cycle	3	1	3
Gemcitabine	2 x per 21-day cycle	3	2	6
Carboplatin + docetaxel[9]				
Carboplatin	1 x per 21-day cycle	3	1	3
Docetaxel	1 x per 21-day cycle	3	1	3
Carboplatin + pemetrexed[14]				
Carboplatin	1 x per 21-day cycle	4	1	4
Pemetrexed	1 x per 21-day cycle	4	1	4
Simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy.				
Radiotherapy[15]	1-2 x daily	3 - 5	5	15 - 25
Chemotherapy	No specification possible			
Adjuvant treatment: Best supportive care				
Best supportive care	Different from patient to patient			

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

patients with early-stage non-small cell lung cancer. J Thorac Oncol. 2008 Jan;3(1):37-45. doi: 10.1097/JTO.0b013e31815e5d9a

[14] John D. Hainsworth, et al., Phase II trial of preoperative pemetrexed plus carboplatin in patients with stage IB-III nonsquamous non-small cell lung cancer (NSCLC), Lung Cancer, Volume 118, 2018, Pages 6-12, SSN 0169-5002, https://doi.org/10.1016/j.lungcan.2018.01.009

[15] S3 guideline - Prevention, diagnosis, therapy and after-care of lung cancer, version 2.2 - July 2023, AWMF register number: 020-007OL

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Patient populations a) and b)					
Neoadjuvant treatment: Pembrolizumab + platinum-based chemotherapy					
Pembrolizumab + cisplatin + pemetrexed					
Pembrolizumab	200 mg or 400 mg	200 mg 400 mg	2 x 100 mg 4 x 100 mg	4.0 2.0	8 x 100 mg 8 x 100 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	4.0	4 x 50 mg + 4 x 100 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	2 x 500 mg	4.0	8 x 500 mg
Pembrolizumab + cisplatin + gemcitabine					
Pembrolizumab	200 mg or 400 mg	200 mg 400 mg	2 x 100 mg 4 x 100 mg	4.0 2.0	8 x 100 mg 8 x 100 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	4.0	4 x 50 mg + 4 x 100 mg
Gemcitabine	1,000 mg/m² = 1,910 mg	1,910 mg	2 x 1,000 mg	8.0	16 x 1,000 mg
Adjuvant treatment: Pembrolizumab (monotherapy)					
Pembrolizumab	200 mg or 400 mg	200 mg 400 mg	2 x 100 mg 4 x 100 mg	13.0 7.0	26 x 100 mg 28 x 100 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy:					
Patient population a)					
Neoadjuvant treatment: Nivolumab + platinum-based chemotherapy					
Nivolumab + carboplatin + paclitaxel					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Nivolumab	360 mg	360 mg	3 x 120 mg	3	9 x 120 mg
Carboplatin	AUC 5 = 700.7 mg – AUC 6 = 840.9 mg	700.7 mg – 840.9 mg	1 x 600 mg + 1 x 150 mg – 2 x 450 mg	3	3 x 600 mg + 3 x 150 mg – 6 x 450 mg
Paclitaxel	175 mg/m² = 334.3 mg – 200 mg/m² = 382 mg	334.3 mg – 382 mg	1 x 150 mg + 2 x 100 mg – 1 x 300 mg + 3 x 30 mg	3	3 x 150 mg + 6 x 100 mg – 3 x 300 mg + 9 x 30 mg
Nivolumab + cisplatin + pemetrexed					
Nivolumab	360 mg	360 mg	3 x 120 mg	3	9 x 120 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	3	3 x 50 mg + 3 x 100 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	2 x 500 mg	3	6 x 500 mg
Nivolumab + cisplatin + gemcitabine					
Nivolumab	360 mg	360 mg	3 x 120 mg	3	9 x 120 mg
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	3	3 x 50 mg + 3 x 100 mg
Gemcitabine	1,000 mg/m² = 1,910 mg - 1,250 mg/m² = 2,387.5 mg	1,910 mg – 2,387.5 mg	2 x 1,000 mg – 2 x 200 mg + 2 x 1,000 mg	6	12 x 1,000 mg – 12 x 200 mg + 12 x 1,000 mg
Adjuvant treatment: Best supportive care					
Best supportive care	Different from patient to patient				
Patient population b)					
Neoadjuvant treatment: Patient-individual therapy with selection of preoperative (neoadjuvant) systemic chemotherapy with selection of					
cisplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cisplatin + vinorelbine[9]					
Cisplatin	80 mg/m² = 152.8 mg	152.8 mg	1 x 10 mg + 1 x 50 mg + 1 x 100 mg	3	3 x 10 mg + 3 x 50 mg + 3 x 100 mg
Vinorelbine	30 mg/m² = 57.3 mg	57.3 mg	1 x 10 mg + 1 x 50 mg	6	6 x 10 mg + 6 x 50 mg
Cisplatin + paclitaxel[10]					
Cisplatin	60 mg/m² = 114.6 mg	114.6 mg	2 x 10 mg + 1 x 100 mg	2	4 x 10 mg + 2 x 100 mg
Paclitaxel	175 mg/m² = 334.3 mg	334.3 mg	1 x 150 mg + 2 x 100 mg	2	2 x 150 mg + 4 x 100 mg
Cisplatin + gemcitabine[9]					
Cisplatin	75 mg/m² = 143.3 mg – 80 mg/m² = 152.8 mg	143.3 mg – 152.8 mg	1 x 50 mg + 1 x 100 mg – 1 x 10 mg + 1 x 50 mg + 1 x 100 mg	3	3 x 50 mg + 3 x 100 mg – 3 x 10 mg + 3 x 50 mg + 3 x 100 mg
Gemcitabine	1,250 mg/m² = 2,387.5 mg	2,387.5 mg	2 x 200 mg + 2 x 1,000 mg	6	12 x 200 mg + 12 x 1,000 mg
Cisplatin + docetaxel[11]					
Cisplatin	80 mg/m² = 152.8 mg	152.8 mg	1 x 10 mg + 1 x 50 mg + 1 x 100 mg	3	3 x 10 mg + 3 x 50 mg + 3 x 100 mg
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	3	3 x 160 mg
Cisplatin + pemetrexed[12]					
Cisplatin	75 mg/m² = 143.3 mg	143.3 mg	1 x 50 mg + 1 x 100 mg	3	3 x 50 mg + 3 x 100 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	2 x 500 mg	3	6 x 500 mg
Carboplatin in combination with a third-generation cytostatic (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)					
Carboplatin + vinorelbine					
No specification possible					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Carboplatin + paclitaxel[9]					
Carboplatin	AUC 5 = 700.7 mg	700.7 mg	1 x 600 mg + 1 x 150 mg	3	3 x 600 mg + 3 x 150 mg
Paclitaxel	175 mg/m^2 = 334.3 mg	334.3 mg	1 x 150 mg + 2 x 100 mg	3	3 x 150 mg + 6 x 100 mg
Carboplatin + gemcitabine[13]					
Carboplatin	AUC 5.5 = 771 mg	771 mg	1 x 600 mg + 1 x 150 mg + 1 x 50 mg	3	3 x 600 mg + 3 x 150 mg + 3 x 50 mg
Gemcitabine	1,000 mg/m^2 = 1,910 mg	1,910 mg	2 x 1,000 mg	6	12 x 1,000 mg
Carboplatin + docetaxel[9]					
Carboplatin	AUC 6 = 840.9 mg	840.9 mg	2 x 450 mg	3	6 x 450 mg
Docetaxel	75 mg/m^2 = 143.3 mg	143.3 mg	1 x 160 mg	3	3 x 160 mg
Carboplatin + pemetrexed[14]					
Carboplatin	AUC 6 = 840.9 mg	840.9 mg	2 x 450 mg	4	8 x 450 mg
Pemetrexed	500 mg/m^2 = 955 mg	955 mg	2 x 500 mg	4	8 x 500 mg
Simultaneous radiochemotherapy with platinum-based (cisplatin or carboplatin) combination chemotherapy.					
Radiotherapy[15]	1.5 Gy – 1.8 Gy	1.8 Gy – 3 Gy	1 x 1.8 Gy – 2 x 1.5 Gy	15 - 25	25 x 1.8 Gy – 30 x 1.5 Gy
Chemotherapy	No specification possible				
Adjuvant treatment: Best supportive care					
Best supportive care	Different from patient to patient				

Costs:

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 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. 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Radiotherapy

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

Designation of the therapy	Designation of the service	Number	Costs per unit	Costs/ patient/ year
Appropriate comparator therapy:				
Radiotherapy	Irradiation with a linear accelerator for malignant diseases or space-occupying processes of the central nervous system (GOP: 25321)	25 - 30	€ 114.57	€ 2,864.25 - € 3,437.10
	Computer-aided treatment planning for percutaneous radiotherapy with individual dose planning for irregular fields with individual blocks, multi-lamella collimator, non-coplanar fields and/or 3D planning (GOP: 25342)	1	€ 566.14	€ 566.14

Costs of the medicinal products:

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:					
Pembrolizumab 100 mg	1 CIS	€ 2,743.07	€ 2.00	€ 153.37	€ 2,587.70
Cisplatin 100 mg	1 CIS	€ 84.13	€ 2.00	€ 9.22	€ 72.91
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Pemetrexed 500 mg	1 PCI	€ 567.62	€ 2.00	€ 26.40	€ 539.22
Gemcitabine 1000 mg	1 PIS	€ 102.35	€ 2.00	€ 10.62	€ 89.73
Best supportive care	Different from patient to patient				
Appropriate comparator therapy:					
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 450 mg	1 CIS	€ 228.24	€ 2.00	€ 10.29	€ 215.95
Carboplatin 150 mg	1 CIS	€ 83.06	€ 2.00	€ 3.40	€ 77.66
Carboplatin 50 mg	1 CIS	€ 34.66	€ 2.00	€ 1.11	€ 31.55
Cisplatin 100 mg	1 CIS	€ 84.13	€ 2.00	€ 9.22	€ 72.91
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Cisplatin 10 mg	1 CIS	€ 18.60	€ 2.00	€ 0.35	€ 16.25
Docetaxel 160 mg	1 CIS	€ 515.78	€ 2.00	€ 23.94	€ 489.84
Gemcitabine 1000 mg	1 PIS	€ 102.35	€ 2.00	€ 10.62	€ 89.73
Gemcitabine 200 mg	1 CIS	€ 28.85	€ 2.00	€ 0.83	€ 26.02
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 85.05	€ 1,459.91
Paclitaxel 300 mg	1 CIS	€ 847.03	€ 2.00	€ 39.66	€ 805.37
Paclitaxel 150 mg	1 CIS	€ 428.97	€ 2.00	€ 19.82	€ 407.15
Paclitaxel 100 mg	1 CIS	€ 289.47	€ 2.00	€ 13.20	€ 274.27
Paclitaxel 30 mg	1 CIS	€ 94.15	€ 2.00	€ 3.93	€ 88.22
Pemetrexed 500 mg	1 PCI	€ 567.62	€ 2.00	€ 26.40	€ 539.22
Vinorelbine 50 mg	1 CIS	€ 152.64	€ 2.00	€ 6.71	€ 143.93
Vinorelbine 10 mg	1 CIS	€ 38.90	€ 2.00	€ 1.31	€ 35.59
Best supportive care	Different from patient to patient				
Abbreviations: CIS = concentrate for the preparation of an infusion solution, PCI = powder for a concentrate for the preparation of an infusion solution; PIS = powder for the preparation of an infusion solution					

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<u>Costs for additionally required SHI services:</u>

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 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.

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant 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
Medicinal product to be assessed:							
Pembrolizumab + platinum-based chemotherapy (neoadjuvant treatment)							
Pembrolizumab + cisplatin + pemetrexed							
Pemetrexed							
Dexamethasone[16] 2 x 4 mg	50 x 4 mg TAB	€ 45.28	€ 2.00	€ 2.69	€ 40.59	12	€ 40.59
Folic acid[17] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.29	€ 0.86	€ 1.97	€ 14.46	91	€ 14.46 - € 28.92
Vitamin B12[16] 1,000 µg/day, every 3 cycles	5 x 1,000 µg SFI	€ 4.95	€ 0.25	€ 0.22	€ 4.48	3	€ 4.48
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.							

[16] Fixed reimbursement rate

[17] 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.

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
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 103.20	€ 5.16	€ 3.57	€ 94.47	4	€ 94.47
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	4	€ 34.98
	10 x 1000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		€ 40.10
Pembrolizumab + cisplatin + gemcitabine							
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.							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 103.20	€ 5.16	€ 3.57	€ 94.47	4	€ 94.47
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66	4	€ 34.98
	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05		€ 40.10
Appropriate comparator therapy:							
Nivolumab + platinum-based chemotherapy (neoadjuvant treatment)							
Nivolumab + carboplatin + paclitaxel							
Paclitaxel							
Dexamethasone[16] 2 x 20 mg	10 x 20 mg TAB	€ 32.42	€ 2.00	€ 0.00	€ 30.42	3	€ 30.42
Dimetindene IV 1 mg/10 kg BW = 7.8 mg	5 x 4 mg SFI	€ 23.72	€ 2.00	€ 5.02	€ 16.70	3	€ 33.40
Cimetidine 300 mg IV	10 x 200 mg AMP	€ 19.80	€ 2.00	€ 0.40	€ 17.40	3	€ 17.40
Nivolumab + cisplatin + pemetrexed							

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
Pemetrexed							
Dexamethasone[16] 2 x 4 mg	20 x 4 mg TAB	€ 24.61	€ 2.00	€ 1.05	€ 21.56	9	€ 21.56
Folic acid[17] 350 – 1,000 µg/day	100 x 400 µg TAB	€ 17.29	€ 0.86	€ 1.97	€ 14.46	70	€ 14.46 - € 28.92
Vitamin B12[16] 1,000 µg/day, every 3 cycles	5 x 1,000 µg SFI	€ 4.95	€ 0.25	€ 0.22	€ 4.48	3	€ 4.48
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.							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 103.20	€ 5.16	€ 3.57	€ 94.47	3	€ 94.47
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	3	€ 20.05 -
	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66		€ 34.98
Nivolumab + cisplatin + gemcitabine							
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.							
Hydration and forced diuresis							
Mannitol 10% infusion solution, 37.5 g/day	10 x 500 ml INF	€ 103.20	€ 5.16	€ 3.57	€ 94.47	3	€ 94.47
Sodium chloride 0.9% Inf. Solution, 3 - 4.4 l/day	10 x 1,000 ml INF	€ 23.10	€ 1.16	€ 1.89	€ 20.05	3	€ 20.05 -
	10 x 500 ml INF	€ 13.28	€ 0.66	€ 0.96	€ 11.66		€ 34.98
Abbreviations: INF = infusion solution; AMP = ampoules; SFI = solution for injection; TAB = tablets							

As the appropriate comparator therapy for patient population b) in the present case was exceptionally determined as the off-label use of medicinal products, no statement can be made as to whether there are regular differences in the necessary use of medical treatment or in the prescription of other services when using the medicinal product to be assessed compared with the appropriate comparator therapy according to the product information. Therefore, no costs for additionally required SHI services are taken into account here.

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 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 cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. 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 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.

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from

the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution; last revised: September 2024

b) Adults with resectable non-small cell lung carcinoma with tumour cell PD-L1 expression < 1% at high risk of recurrence; neoadjuvant and adjuvant treatment

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for pembrolizumab (Keytruda); Keytruda 25 mg/ml concentrate for the preparation of an infusion solution; last revised: September 2024

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

On 19 April 2024, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

The Subcommittee on Medicinal Products determined the appropriate comparator therapy for the assessment procedure at its session on 7 May 2024.

By letter dated 30 April 2024 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 pembrolizumab. The appropriate comparator therapy determined for the assessment procedure was submitted to IQWiG on 8 May 2024 in addition to the letter of 30 April 2024.

The dossier assessment by the IQWiG was submitted to the G-BA on 30 July 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 August 2024. The deadline for submitting statements was 22 August 2024.

The oral hearing was held on 9 September 2024.

By letter dated 10 September 2024, 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 September 2024.

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 8 October 2024, and the proposed draft resolution was approved.

At its session on 17 October 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	7 May 2024	Determination of the appropriate comparator therapy
Working group Section 35a	3 September 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 September 2024	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	17.09.2024; 30.09.2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	8 October 2024	Concluding discussion of the draft resolution
Plenum	17 October 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 17 October 2024

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

Prof. Hecken