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) Nivolumab (new therapeutic indication: non-small cell lung cancer, PD-L1 expression ≥ 1%, neoadjuvant therapy, combination with platinum-based chemotherapy)

of 1 February 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 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 nivolumab (Opdivo) was listed for the first time on 15 July 2015 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 26 June 2023, nivolumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 24 July 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient nivolumab with the new therapeutic indication: "OPDIVO in combination with platinum-based chemotherapy is indicated for the

neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.".

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 November 2023 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on 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 as the addendum to the benefit assessment prepared by IQWiG, the G-BA decided on the question on whether an additional benefit of nivolumab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. 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 IQWiG according to the General Methods was not used in the benefit assessment of nivolumab – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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

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

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

Opdivo in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%.

Therapeutic indication of the resolution (resolution of 1 February 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy</u>

Appropriate comparator therapy for nivolumab in combination with a platinum-based therapy for 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)

  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.

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 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.

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

on 1. Besides nivolumab, no other medicinal products are approved for the present therapeutic indication.

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

on 3. No resolutions are available.

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.

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. In this respect, the appropriate comparator therapy was determined on the condition that a decision in favour of neoadjuvant therapy was made.

In addition, for neoadjuvant therapy of resectable NSCLC, the guidelines, the written statement of the AkdÄ and the joint written statement of four scientific-medical societies on the question of comparator therapy unanimously refer to systemic neoadjuvant chemotherapy. However, there are hardly any specific recommendations in the guidelines with regard to the active ingredients used in chemotherapy. In the written statement of the AkdÄ and the scientific-medical societies, platinum-based combination chemotherapy is presented as the standard. The selection of active ingredients depends on patient-individual criteria, in particular with regard to existing comorbidities and tumour histology. 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. Effective combinations include the platinum derivatives cisplatin or carboplatin in combination with vinorelbine, paclitaxel, docetaxel, gemcitabine or pemetrexed

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 present benefit assessment 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. This applies in particular to stage IIIA, for which systemic chemotherapy and simultaneous radiochemotherapy are equally suitable options. In contrast, in the presence of a Pancoast tumour, simultaneous radiochemotherapy is the treatment of first choice according to the unanimous treatment recommendations in the guidelines. In addition, simultaneous radiochemotherapy can be considered as an option for preoperative therapy in selected cases of advanced tumour stages that are classified as potentially R0-resectable. 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 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 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. Overall, there are no other approved medicinal products available in this therapeutic indication apart from the medicinal product to be assessed here.

On the basis of evidence-based guideline recommendations[1,2,3], the statements of the scientific-medical societies in the present benefit assessment procedure and the written statement of the AkdÄ on the question of comparator therapy, the above-mentioned active ingredients or combinations of active ingredients are considered the therapy standard according to the generally recognised state of medical knowledge in the therapeutic indication to be assessed. It is therefore appropriate to determine the off-label use of medicinal products as an appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3, number 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

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.

[1] 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 2.0 [online]. AWMF register number 020-007OL. Berlin (GER): Oncology guideline programme; 2022.

[2] Daly ME, Singh N, Ismaila N, Antonoff MB, Arenberg DA, Bradley J, et al. Management of stage III non-small-cell lung cancer: ASCO Guideline. J Clin Oncol 2022;40(12):1356-1384.

[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.

Change of the appropriate comparator therapy:

The appropriate comparator therapy for the present benefit assessment procedure was originally determined as follows:

Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy

Appropriate comparator therapy for nivolumab in combination with a platinum-based therapy for neoadjuvant treatment:

Patient-individual therapy with selection of:

- preoperative (neoadjuvant) systemic chemotherapy with selection of
  - Cisplatin in combination with vinorelbine

  and
  - cisplatin in combination with paclitaxel (only for extensive-stage patients)

  and
- simultaneous radiochemotherapy with cisplatin in combination with vinorelbine as chemotherapy,

taking into account the tumour stage, the presence of a Pancoast tumour and the feasibility of an R0 resection.

This appropriate comparator therapy was determined under the effects of the ruling of the Federal Social Court (FSC) of 22 February 2023. According to the FSC's comments on this ruling (file ref.: B 3 KR 14/21 R), medicinal products that do not have a marketing authorisation for the present indication and whose prescribability in off-label use has also not been recognised by the G-BA in the Pharmaceuticals Directive are generally not considered as appropriate comparator therapy in the narrower sense of Section 2, paragraph 1, sentence 3, Section 12 SGB V.

Within the scope of this provision, it was to be noted that medicinal therapies not approved for the neoadjuvant and adjuvant treatment of resectable NSCLC both approved and unapproved medicinal therapies are mentioned by the scientific-medical societies and/or the AkdÄ according to Section 35a, paragraph 7, sentence 4 SGB V.

With the entry into force of the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) on 27 July 2023, the G-BA can exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy in accordance with Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

In view of the fact that in the present therapeutic indication, off-label use of medicinal products is considered, also taking into account the statements of scientific-medical societies on the question of comparator therapy in the present procedure, a review of the appropriate comparator therapy under the regulations after the entry into force of the ALBVVG (Act to Combat Supply Shortages and Improve the Supply of Medicines) was necessary. In the course of this, the appropriate comparator therapy was changed for the present resolution.

The originally determined appropriate comparator therapy was determined on the assumption that cisplatin in combination with vinorelbine and cisplatin in combination with paclitaxel, each for neoadjuvant systemic chemotherapy, and cisplatin in combination with vinorelbine for simultaneous radiochemotherapy are treatments that are covered by the

marketing authorisation for the respective active ingredients. This assumption was based on an interpretation of the corresponding product information for the active ingredients, whereby the product information did not specifically state a marketing authorisation for the neoadjuvant treatment of resectable NSCLC.

As part of the review of the appropriate comparator therapy for the present resolution, the G-BA requested information from the competent national regulatory authority, the BfArM, on the authorisation status of cisplatin in combination with various third-generation cytostatics with regard to the neoadjuvant treatment of resectable NSCLC. In this regard, the BfArM has stated that no medicinal products have been approved for this indication to date, not even in combination therapy with cisplatin.[4]

The change in the appropriate comparator therapy means that the results of the CheckMate 816 study presented by the pharmaceutical company in the dossier can be used for the PD-L1-positive sub-population without any limitation with regard to the comparator therapies of the originally determined appropriate comparator therapy. The results of the CheckMate 816 study were analysed by IQWiG in the addendum to the dossier assessment. In addition, these were the subject of the statements, which is why the change in the appropriate comparator therapy does not necessitate a renewed conduct of the benefit assessment procedure.

[4] BfArM. Information on the marketing authorisation of cisplatin doublets in NSCLC. Reply letter dated 19.01.2024.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of nivolumab in combination with platinum-based chemotherapy is assessed as follows:

Hint for a non-quantifiable additional benefit

Justification:

For the proof of additional benefit of nivolumab in combination with platinum-based chemotherapy, the pharmaceutical company presented the results of the CheckMate 816 study.

CheckMate 816 is a multicentre, open-label, randomised controlled trial comparing nivolumab in combination with platinum-based chemotherapy with platinum-based chemotherapy. The study enrolled adult patients with histologically confirmed and resectable stage IB (tumour size ≥ 4 cm), II or IIIA NSCLC (each according to the 7th edition of the staging criteria of the International Association for the Study of Lung Cancer (IASLC)).

Furthermore, patients should have an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1 for enrolment in the study.

Patients with known EGFR mutations or ALK translocation and with previous chemotherapy or other cancer therapy at an early stage of NSCLC were excluded from the study. Tumour cell PD-L1 expression had to be determined for enrolment in the study.

The original study protocol provided for randomisation in a 1:1 ratio into the following 2 treatment arms: Nivolumab + ipilimumab (arm A) vs platinum-based chemotherapy (arm B). With revised protocol 02 of 06.07.2017, a 3rd treatment arm was introduced (nivolumab + platinum-based chemotherapy, arm C) and randomisation was carried out in a 1:1:1 ratio. With another updated protocol version 03 dated 21.09.2018, randomisation in the nivolumab + ipilimumab arm was then stopped and only randomised in the two remaining arms in a 1:1 ratio. The evaluations presented by the pharmaceutical company in the dossier only include patients who were randomised to treatment arms B and C at the same time.

After initiation of the treatment arm nivolumab + platinum-based chemotherapy (arm C), a total of 358 patients were randomly assigned to the two treatment arms nivolumab + platinum-based chemotherapy or platinum-based chemotherapy. Randomisation was stratified according to tumour cell PD-L1 expression (≥ 1% vs < 1% incl. non-quantifiable), disease stage at the start of study (IB/II vs IIIA) and sex (male vs female).

In the dossier, the pharmaceutical company presented the data of a sub-population with tumour cell PD-L1 expression of ≥ 1% (PD-L1-positive population). This sub-population comprises 89 patients in each of the two arms.

The treatment options for platinum-based chemotherapy in the intervention arm were cisplatin + gemcitabine (for squamous cell carcinoma), cisplatin + pemetrexed (for non-squamous cell carcinoma) or carboplatin + paclitaxel. In the comparator arm, the principal investigator had 2 further treatment regimens to choose from in addition to the options of the intervention arm: cisplatin + vinorelbine and cisplatin + docetaxel. The chemotherapy regimen of carboplatin + paclitaxel was only introduced in the intervention and comparator arm with the revised protocol 03 of 21.09.2018 and the selection did not require any additional justification by the principal investigator. Furthermore, patients for whom treatment with cisplatin was unsuitable and the reasons for this were documented could receive carboplatin instead of cisplatin.

In the CheckMate 816 study, treatment was administered for up to 3 cycles lasting 3 weeks each or until the occurrence of unacceptable toxicity or therapy discontinuation as decided by the principal investigator or the patients. Within 6 weeks of the end of neoadjuvant treatment, patients who were classified as operable underwent surgical resection of the tumour. Subsequent optional adjuvant therapy, consisting of up to 4 cycles of chemotherapy and/or radiotherapy lasting 3 weeks each, was at the discretion of the principal investigator. Possible adjuvant treatment regimens corresponded to the chemotherapy options of the neoadjuvant treatment in the comparator arm

The study is being conducted in 111 study sites in Asia, Europe, and North and South America. The study was launched in March 2017 and is currently ongoing.

The primary endpoints of the CheckMate 816 study are event-free survival (EFS) and pathological complete remission (pCR). Patient-relevant secondary endpoints include endpoints in the categories of overall survival, morbidity and side effects.

For the CheckMate 816 study, 3 pre-specified data cut-offs are available:

- 1st data cut-off with database lock on 16.09.2020: Analysis of the pCR
- 2. data cut-off with database lock on 20.10.2021: 1. interim analysis of EFS and overall survival
- 3. data cut-off with database lock on 14.10.2022: 2. interim analysis of EFS and overall survival

The present benefit assessment is based on the results of the 3rd data cut-off with database lock on 14.10.2022.

Limitations of the CheckMate 816 study

No randomised allocation of the chemotherapy components

In the CheckMate 816 study, the choice of platinum component (carboplatin or cisplatin) was made by the principal investigator prior to randomisation. However, the selection of the additional chemotherapy component (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) by the principal investigator only took place after randomisation. Thus, no randomised allocation of the study medication could be achieved in the study in its entirety. In addition, the options cisplatin + vinorelbine and cisplatin + docetaxel were only available for the comparator arm. As a result, no valid subgroup analyses can be carried out to investigate potentially different effects, depending on the other chemotherapy components.

Size of the study population

The present sub-population (PD-L1-positive population) comprises 178 patients with 89 patients from each of the 2 study arms. In view of the heterogeneous patient population and the different options for individual treatment decisions, the study population or sub-population is relatively small. In this regard, the relatively small patient population analysed was also noted in the statement by the scientific-medical societies.

Percentage of immune checkpoint inhibitors in subsequent therapies

During the observation period of the study, 18 (20.2%) of the patients in the intervention arm and 36 (40.4%) in the control arm received systemic subsequent therapy. The main systemic subsequent therapies used were immunotherapies, targeted therapies and chemotherapies. In this respect, a relatively low percentage of immune checkpoint inhibitors is noticeable. In the intervention arm, 3 patients and in the control arm 21 patients subsequently received an

immune checkpoint inhibitor, which corresponds to a percentage of 16.7% in the intervention arm and 58.3% in the control arm in relation to the patients with systemic subsequent therapy. In this regard, it is also noted in the statement by the scientific-medical societies that the rate of patients in the control arm receiving immune checkpoint inhibitors in relapse appears to be relatively low. Immune checkpoint inhibitors are therapy standard in the treatment of advanced/ metastatic NSCLC.

R0 resection rate

According to the information provided by the pharmaceutical company in the dossier, the percentage of operations performed was 84.3% in the intervention arm and 74.2% in the control arm. The percentage of successful operations (R0 resection) was 76.4% in the intervention arm and 60.7% in the control arm. Against the background of the present therapeutic indication, which is based on resectable non-small cell lung cancer, these rates of R0 resections appear relatively low. In this regard, it is also noted in the statement of the scientific-medical societies that the results of the operation (R0 rate) are lower than in the German healthcare context.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there is a statistically significant difference in favour of nivolumab in combination with platinum-based chemotherapy, which is assessed as a significant advantage. Median survival time was not reached in either study arm at the present data cut-off.

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 event-free survival (EFS) endpoint from the CheckMate 816 study is used as an approximation to illustrate the failure of the curative therapeutic approach.

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 CheckMate 816 study as the time from randomisation to the occurrence of one of the following events: Progression of disease precluding surgery, progression or recurrence after surgery (based on blinded independent centralised review [BICR] or death from any cause.

In addition, the pharmaceutical company submitted a further operationalisation of the EFS endpoint in an SAP (AMNOG-SAP) created specifically a priori for the early benefit assessment. Accordingly, the EFS endpoint was operationalised as the time from randomisation to the first occurrence of one of the following events:

- Progression of the disease, adverse event or any other event that rules out surgery
- Failed R0 resection of the tumour (R1, R2, Rx)
- Recurrence after successful R0 resection
- Recurrence in patients without surgery
- Death from any cause

Progression of the disease was not categorised as an event if surgery could still take place.

With regard to the endpoint component "Progression of the disease, adverse event or any other event that rules out surgery", it should be noted that the pharmaceutical company does provide examples of "any other event" in the AMNOG-SAP, such as toxicity, deterioration of health status or refusal of surgery. However, information on the events that actually occurred was not provided, which means that it remains unclear which events may have occurred at the discretion of the principal investigator. The percentage of "other events" totals 20% of all EFS events.

With regard to the endpoint component "Recurrence in patients without surgery", it should also be noted that it is unclear how it should be ensured that patients are disease-free.

Irrespective of the uncertainties mentioned, the evaluations are considered suitable for showing the failure of the curative therapeutic approach in accordance with the operationalisation according to the AMNOG-SAP and are 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 is a statistically significant difference in favour of nivolumab in combination with platinum-based chemotherapy, both for the event rate and for the time-dependent evaluation, which is considered a clear advantage.

Health status (EQ-5D VAS)

The health status was assessed in the CheckMate 816 study using the EQ-5D visual analogue scale (VAS).

The pharmaceutical company shall submit responder analyses for the time to permanent deterioration, defined as the decrease of the corresponding score by at least the response criterion without subsequent improvement above the response criterion in one of the following surveys. According to the pharmaceutical company, "permanent" refers to all further follow-up surveys. For patients for whom no more data was available after the first deterioration, the health status was assessed as permanently deteriorated and no censoring was carried out.

According to the study protocol, the health status is to be recorded until death, the end of study or withdrawal of the consent form. Information on the actual observation period for the PD-L1-positive population for this endpoint is not available. It is therefore unclear whether it is appropriate to speak of a "permanent deterioration" in this setting. In addition, the percentage of patients with "permanent deterioration" who were either not surveyed after the 1st deterioration or for whom follow-up surveys were missing is high (37.5% [intervention arm] vs 22.7% [comparator arm]). There is therefore not a single confirmation of deterioration in these patients.

The evaluation of time to first deterioration is used for the present benefit assessment.

For the endpoint of health status, there is no statistically significant difference between the treatment groups.

Quality of life

Data on health-related quality of life were not collected in the CheckMate 816 study.

Side effects

Adverse events (AEs) in total

In the study, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAEs), therapy discontinuations due to Aes (discontinuation of at least 1 active ingredient component)

There were no statistically significant differences between the treatment arms for the endpoints of SAEs and therapy discontinuations due to AEs.

Severe AEs (CTCAE grade ≥ 3)

For severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference to the advantage of nivolumab in combination with platinum-based chemotherapy.

Specific AEs

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

For the assessment of immune-mediated AEs, the endpoint of AEs of special interest designated by the pharmaceutical company as "select AEs" is used. This is a selection of categories and preferred terms (PTs) that belong to the typical immune-mediated AEs and for which treatment of the AEs with immunosuppression (e.g. with corticosteroids) could be necessary, but not mandatory. This operationalisation is considered a sufficient approximation for immune-mediated AEs.

For the immune-mediated SAEs and immune-mediated severe AEs (CTCAE grade ≥ 3), there is no statistically significant difference between the treatment groups.

Other specific AEs

Blood and lymphatic system disorders (CTCAE grade ≥ 3), metabolism and nutrition disorders (CTCAE grade ≥ 3)

In detail, there were statistically significant differences in the area of specific AEs to the advantage of nivolumab in combination with platinum-based chemotherapy for blood and lymphatic system disorders (CTCAE grade ≥ 3) and metabolism and nutrition disorders (CTCAE grade ≥ 3).

The overall assessment of the results on side effects shows an advantage of nivolumab in combination with platinum-based chemotherapy for severe AEs (CTCAE grade ≥ 3). In detail, there are advantages in the specific AEs.

<u>Overall assessment</u>

For the benefit assessment of nivolumab in combination with platinum-based chemotherapy, data are available from the open-label, randomised CheckMate 816 study on mortality, morbidity and side effects compared to platinum-based chemotherapy.

For overall survival, there is a statistically significant difference in favour of nivolumab in combination with platinum-based chemotherapy, which is assessed as a significant advantage. Median survival time was not reached in either study arm at the present data cut-off.

In the morbidity endpoint category, there was a statistically significant difference in the endpoint "failure of the curative therapeutic approach" (event-free survival, EFS) to the advantage of nivolumab in combination with platinum-based chemotherapy, which is considered a significant advantage. There was no statistically significant difference between the treatment arms for the endpoint of health status (measured using EQ-5D-VAS).

Data on health-related quality of life were not collected in the CheckMate 816 study.

In terms of side effects, there is an advantage of nivolumab in combination with platinum-based chemotherapy for severe AEs (CTCAE grade ≥ 3). In detail, there are advantages in the specific AEs.

In the overall analysis, there are significant advantages in the endpoints "overall survival" and "failure of the curative therapeutic approach" and also an advantage in terms of side effects. These advantages are not offset by any disadvantages. No data were collected with regard to the endpoints on health-related quality of life. The effects indicate a significant improvement that can be achieved with nivolumab in combination with platinum-based chemotherapy. Against the background of relevant limitations in the data basis, however, the extent of the additional benefit cannot be quantified with certainty. With regard to transferability to the German healthcare context, there are relevant uncertainties, which are due on the one hand to a relatively low percentage of standard therapies in the subsequent therapies and on the other to a conspicuously lower rate of successful operations (R0 resections).

As a result, the G-BA determined a non-quantifiable additional benefit for nivolumab in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC with tumour cell PD-L1 expression ≥ 1% in adults at a high risk of recurrence.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the open-label, randomised, ongoing phase III CheckMate 816 study.

The risk of bias at the study level is rated as high. The study and the present sub-population are relatively small in view of the heterogeneous patient population and different options for individual treatment decisions. No randomised allocation of all components of platinum-based chemotherapy was carried out, which is why no valid subgroup analyses could be carried out in some cases.

The endpoint-specific risk of bias is assessed as low for the endpoints of overall survival and failure of the curative therapeutic approach.

Therefore, overall, the reliability of data for the additional benefit determined is classified in the "hint" category.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Opdivo with the active ingredient nivolumab in a new therapeutic indication: The new therapeutic indication is:

"OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1%".

The G-BA defined an appropriate comparator therapy as a patient-individual therapy with a choice of different platinum-based chemotherapies and the option of simultaneous radiochemotherapy for certain subtypes of non-small cell lung cancer (NSCLC).

The results of the CheckMate 816 study were submitted by the pharmaceutical company for the benefit assessment. The CheckMate 816 study is a randomised controlled trial in which patients were treated with neoadjuvant therapy (preoperatively) before the intended operation to resect the tumour. Nivolumab in combination with platinum-based chemotherapy was compared with platinum-based chemotherapy. The assessment is based on a sub-population of the study (tumour cell PD-L1 expression of ≥ 1%), which comprises 89 patients in each of the two study arms.

The study results show clear advantages in the endpoints "overall survival" and "failure of the curative therapeutic approach". There is also an advantage in terms of side effects. These

advantages are not offset by any disadvantages. Data on health-related quality of life were not collected. Overall, the effects indicate a significant improvement that can be achieved with nivolumab in combination with platinum-based chemotherapy. Against the background of relevant limitations in the data basis, however, the extent of the additional benefit cannot be quantified with certainty. The reliability of data is classified in the "hint" category.

As a result, the G-BA identified a hint for a non-quantifiable additional benefit of nivolumab in combination with platinum-based chemotherapy for the neoadjuvant treatment of resectable NSCLC with tumour cell PD-L1 expression ≥ 1% in adults at a high risk of recurrence.

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

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

The G-BA bases its resolution on the information from the dossier of the pharmaceutical company. It should be noted that the patient numbers presented are likely to be an underestimate overall. This results from the fact that the limitation to patients who have received neoadjuvant therapy in the previous healthcare context is inappropriate to identify those patients for whom neoadjuvant treatment with nivolumab is an option.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Opdivo (active ingredient: nivolumab) at the following publicly accessible link (last access: 2 October 2023):

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

Treatment with nivolumab 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 cancer, 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 European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

The training material contains, in particular, information and warnings about immune-mediated side effects as well as 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 January 2024).

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 shown for nivolumab in combination with platinum-based chemotherapy correspond to the treatment regimens used in the CheckMate 816 approval study. 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 for the therapy options defined as appropriate comparator therapy in the present therapeutic indication. 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.

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).[5]

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) [6] and the mean standard serum creatinine concentration (women: 0.75 mg/dl, men: 0.9 mg/dl).[7]

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.

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

[6] 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

[7] DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 18 January 2024

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed: Nivolumab + platinum-based chemotherapy				
Nivolumab	1 x per 21-day cycle	3	1	3
+ paclitaxel	1 x per 21-day cycle	3	1	3
+ carboplatin	1 x per 21-day cycle	3	1	3
	or			
+ pemetrexed	1 x per 21-day cycle	3	1	3
+ cisplatin	1 x per 21-day cycle	3	1	3
	or			
+ cisplatin	1 x per 21-day cycle	3	1	3
+ gemcitabine	2 x per 21-day cycle	3	2	6
Appropriate comparator therapy:				
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[11]				
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
Paclitaxel	1 x per 21-day cycle	2	1	2
Cisplatin + gemcitabine[11]				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Cisplatin	1 x per 21-day cycle	3	1	3
Gemcitabine	2 x per 21-day cycle	3	2	6
Cisplatin + docetaxel[12]				
Cisplatin	1 x per 21-day cycle	3	1	3
Docetaxel	1 x per 21-day cycle	3	1	3
Cisplatin + pemetrexed[13]				
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[11]				
Carboplatin	1 x per 21-day cycle	3	1	3
Paclitaxel	1 x per 21-day cycle	3	1	3
Carboplatin + gemcitabine[14]				
Carboplatin	1 x per 21-day cycle	3	1	3
Gemcitabine	2 x per 21-day cycle	3	2	6
Carboplatin + docetaxel[11]				
Carboplatin	1 x per 21-day cycle	3	1	3
Docetaxel	1 x per 21-day cycle	3	1	3
Carboplatin + pemetrexed[15]				
Carboplatin	1 x per 21-day cycle	4	1	4

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pemetrexed	1 x per 21-day cycle	4	1	4
Simultaneous radiochemotherapy				
Radiotherapy[16]	1-2 x daily	3 - 5	5	15 - 25
Chemotherapy	No specification possible			

Consumption:

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

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: Nivolumab + platinum-based chemotherapy					
Nivolumab	360 mg	360 mg	3 x 120 mg	3	9 x 120 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
+ 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
	or				
+ pemetrexed[8]	500 mg/m² = 955 mg	955 mg	2 x 500 mg	3	6 x 500 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
	or				

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
+ gemcitabine[9]	1,000 mg/m² = 1,910 mg - 1,250 mg/m² = 2,387.5 mg	1,910 mg – 2,387.5 mg	1 x 2,000 mg – 2 x 200 mg + 1 x 2,000 mg	6	6 x 2,000 mg – 12 x 200 mg + 6 x 2,000 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
Appropriate comparator therapy:					
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[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
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[11]					
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 +	3	3 x 50 mg + 3 x 100 mg – 3 x 10 mg +

[9] Only for patients with a squamous epithelial histology

[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

[11] 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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
			1 x 50 mg + 1 x 100 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 + 1 x 2,000 mg	6	12 x 200 mg + 6 x 2,000 mg
Cisplatin + docetaxel[12]					
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[13]					
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					
Carboplatin + paclitaxel[11]					
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/m² = 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[14]					
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

[12] 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

[13] 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

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Gemcitabine	1,000 mg/m² = 1,910 mg	1,910 mg	1 x 2,000 mg	6	6 x 2,000 mg
Carboplatin + docetaxel[11]					
Carboplatin	AUC 6 = 840.9 mg	840.9 mg	2 x 450 mg	3	6 x 450 mg
Docetaxel	75 mg/m² = 143.3 mg	143.3 mg	1 x 160 mg	3	3 x 160 mg
Carboplatin + pemetrexed[15]					
Carboplatin	AUC 6 = 840.9 mg	840.9 mg	2 x 450 mg	4	8 x 450 mg
Pemetrexed	500 mg/m² = 955 mg	955 mg	2 x 500 mg	4	8 x 500 mg
Simultaneous radiochemotherapy					
Radiotherapy[16]	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				

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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Radiotherapy

Designation of the therapy	Designation of the service	Number	Cost per unit	Costs/ patient/ year
Appropriate comparator therapy:				

[15] 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

[16] 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	Designation of the service	Number	Cost per unit	Costs/ patient/ year
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:					
Nivolumab 120 mg	1 CIS	€ 1,546.96	€ 2.00	€ 85.05	€ 1,459.91
Pemetrexed 500 mg	1 PCI	€ 567.62	€ 2.00	€ 26.40	€ 539.22
Paclitaxel 300 mg	1 CIS	€ 847.48	€ 2.00	€ 39.68	€ 805.80
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
Cisplatin 50 mg	1 CIS	€ 47.73	€ 2.00	€ 4.61	€ 41.12
Cisplatin 100 mg	1 CIS	€ 84.13	€ 2.00	€ 9.22	€ 72.91
Gemcitabine 200 mg	1 CIS	€ 28.85	€ 2.00	€ 0.83	€ 26.02
Gemcitabine 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Carboplatin 600 mg	1 CIS	€ 300.84	€ 2.00	€ 13.74	€ 285.10
Carboplatin 150 mg	1 CIS	€ 83.06	€ 2.00	€ 3.40	€ 77.66
Carboplatin 450 mg	1 CIS	€ 228.24	€ 2.00	€ 10.29	€ 215.95

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
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 2,000 mg	1 CIS	€ 194.23	€ 2.00	€ 8.68	€ 183.55
Gemcitabine 200 mg	1 CIS	€ 28.85	€ 2.00	€ 0.83	€ 26.02
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
Pemetrexed 500 mg	1 PCI	€ 567.62	€ 2.00	€ 26.40	€ 539.22
Vinorelbine 50 mg	1 CIS	€ 156.71	€ 2.00	€ 18.40	€ 136.31
Vinorelbine 10 mg	1 CIS	€ 41.66	€ 2.00	€ 3.84	€ 35.82
Abbreviations: CIS = concentrate for the preparation of an infusion solution, PCI = powder for a concentrate for the preparation of an infusion solution; PIF = powder for the preparation of an infusion solution					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services. Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

As the appropriate comparator therapy 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 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

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

Adults with resectable non-small cell lung cancer with tumour cell PD-L1 expression ≥ 1% at high risk of recurrence; neoadjuvant therapy

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 nivolumab (Opdivo); product information for OPDIVO 10 mg/ml concentrate for the preparation of an infusion solution; last revised: October 2023

3. Bureaucratic costs calculation

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

4. Process sequence

At its session on 27 September 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 July 2023.

On 24 July 2023 the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 28 July 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 26 October 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2023. The deadline for submitting statements was 22 November 2023.

The oral hearing was held on 11 December 2023.

By letter dated 12 December 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 12 January 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 23 January 2024, and the proposed resolution was approved.

At its session on 1 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 September 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	25 July 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	6 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 December 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	20 December 2023 17 January 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	23 January 2024	Concluding discussion of the draft resolution
Plenum	1 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 February 2024

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

Prof. Hecken