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: breast cancer, triple-negative, PD-L1 expression ≥ 10 (CPS), combination with chemotherapy)

of 5 May 2022

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 pembrolizumab (Keytruda) was listed for the first time on 15 February 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 19 October 2021, Keytruda received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 12 November 2021, i.e. at the latest within four weeks after the pharmaceutical company has been notified of the authorisation for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication (in combination with chemotherapy for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 15 February 2022, 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 addenda

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 chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease.

Therapeutic indication of the resolution (resolution of 5 May 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with locally recurrent unresectable or metastatic triple-negative breast cancer whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease

Appropriate comparator therapy for pembrolizumab in combination with chemotherapy:

Systemic therapy containing anthracyclines and/or taxanes, taking into account the marketing authorisation of the medicinal products

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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.

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

on 1. Besides pembrolizumab, medicinal products with the following active ingredients are approved for the present therapeutic indication: 5-fluorouracil, capecitabine, cyclophosphamide, docetaxel, doxorubicin, doxorubicin (liposomal), epirubicin, gemcitabine, ifosfamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vincristine, vinorelbine, bevacizumab and atezolizumab.

on 2. A non-medicinal therapy (radiotherapy) is not considered as an appropriate comparator therapy in the present treatment setting.

on 3. For the present therapeutic indication of pembrolizumab, the following resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V is available:

- Atezolizumab; resolution of 2 April 2020

For the present therapeutic indication of pembrolizumab, the following guidelines of the G-BA for medicinal applications or non-medicinal treatments are available:

- Annex VI to Section K of the Pharmaceuticals Directive - Active ingredients that cannot be prescribed in therapeutic indicationsbeyond the scope of the approval (off-label use):

  Gemcitabine in monotherapy for breast cancer in women

- Guideline Methods Hospital Treatment - Section 4 Excluded Methods:

  Proton therapy for breast cancer

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

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

As the therapeutic indication refers to triple-negative receptor status, endocrine therapies and therapies indicated exclusively for HER2-positive breast cancer are not included.

The evidence for treatment options in the therapeutic indication only partly relates explicitly to the patient population with proven triple-negative breast cancer. Even in the therapy recommendations of the guidelines, the characteristic "triple-negative

breast cancer" is predominantly not explicitly addressed; however, a corresponding differentiation results from separate recommendations for patients with HER2-positive or hormone-receptor-positive breast cancer.

Based on unanimous guideline recommendations, cytotoxic chemotherapy is the standard of care for patients with metastatic or unresectable locally advanced triple receptor-negative breast cancer, and the chemotherapy should contain an anthracycline or a taxane. Both mono-chemotherapy with an anthracycline or a taxane and combination therapy are established treatment options.

Taking into account the respective marketing authorisations, doxorubicin, liposomal doxorubicin, epirubicin and docetaxel, as well as paclitaxel, can be considered as monotherapies.

Combination therapy mainly consists of combining different chemotherapies, including an anthracycline or a taxane, or both in combination. Possible combination chemotherapies according to evidence and marketing authorisation are paclitaxel in combination with an anthracycline (epirubicin + paclitaxel) and in combination with gemcitabine, docetaxel in combination with doxorubicin and in combination with capecitabine, doxorubicin (also liposomal) + cyclophosphamide, epirubicin + cyclophosphamide, epirubicin + docetaxel and epirubicin + paclitaxel.

The aforementioned mono and combination chemotherapies are equally suitable for the implementation of the appropriate comparator therapy.

Combination chemotherapy has stronger effects, but is also fraught with stronger side effects. It may be indicated, for example, in the case of rapid tumour growth or severe discomfort. In addition, the combination with the VEGF antibody bevacizumab can also be considered. Based on the evidence, bevacizumab is a possible therapy option, but not a regular one.

Based on the evidence, anthracyclines and taxanes can also be used if anthracyclines and/or taxanes have already been used in neoadjuvant or adjuvant chemotherapy and a correspondingly late relapse occurs. In determining the appropriate comparator therapy, it was therefore assumed that patients who have already received adjuvant or neoadjuvant taxane and/or anthracycline-based chemotherapy and who have a correspondingly late relapse may in principle be eligible for renewed treatment of metastatic breast cancer with anthracyclines and/or taxanes.

Furthermore, atezolizumab in combination with nab-paclitaxel is also available for first-line treatment. By resolution of 2 April 2020, the G-BA identified a hint for a non-quantifiable additional benefit for adult patients with unresectable locally advanced or metastatic TNBC whose tumours express PD-L1 ≥ 1% and who have not received prior chemotherapy for the treatment of the metastatic disease compared to the appropriate comparator therapy.

A final assessment of the therapeutic significance of atezolizumab in combination with nab-paclitaxel cannot be made at this time and therefore atezolizumab in combination with nab-paclitaxel is not currently determined to be an appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

a) Pembrolizumab in combination with nab-paclitaxel or paclitaxel

There is a hint for a considerable additional benefit for pembrolizumab in combination with nab-paclitaxel or paclitaxel for the treatment of adults with locally recurrent unresectable or metastatic triple-negative breast cancer whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 10) and who have not received prior chemotherapy for the treatment of metastatic disease.

b) Pembrolizumab in combination with chemotherapy other than nab-paclitaxel or paclitaxel

An additional benefit is not proven for pembrolizumab in combination with chemotherapy other than nab-paclitaxel or paclitaxel for the treatment of adults with locally recurrent unresectable or metastatic triple-negative breast cancer whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 10) and who have not received prior chemotherapy for the treatment of metastatic disease.

Justification:

For the benefit assessment, the pharmaceutical company presents results from the ongoing, double-blind, randomised, multicentre phase III KEYNOTE 355 study.

The KEYNOTE 355 study compared pembrolizumab in combination with chemotherapy versus placebo in combination with chemotherapy. The chemotherapy in each case was a chemotherapy of the doctor's choice using paclitaxel, nab-paclitaxel or gemcitabine/ carboplatin.

A total of 847 adult patients with locally relapsing unresectable or metastatic TNBC who had not previously received chemotherapy for this stage of the disease were enrolled in the KEYNOTE 355 study. Patients were allocated to either treatment with pembrolizumab + chemotherapy (N = 566) or placebo + chemotherapy (N = 281), randomised in a 2:1 ratio. Randomisation was stratified by chemotherapy (taxanes vs gemcitabine/ carboplatin), tumour PD-L1 status (CPS ≥ 1 vs CPS < 1) and prior therapy with the same chemotherapy substance class in the (neo)adjuvant setting (yes vs no).

For the benefit assessment, the pharmaceutical company presents results on a sub-population of the KEYNOTE 355 study. This sub-population includes, according to the marketing authorisation, patients whose tumours express PD-L1 with a CPS ≥ 10.

Due to the implementation of the appropriate comparator therapy, only the active ingredients paclitaxel and nab-paclitaxel are additionally considered as chemotherapy in the control arm as well as in the intervention arm. Therefore, no data are available for the combination of pembrolizumab with other approved chemotherapy concomitant active ingredients for the intervention arm.

The relevant sub-population comprised 96 patients in the intervention arm and 47 patients in the comparator arm. The characteristics of the relevant sub-population are mostly comparable between the two treatment arms. The patients were on average about 55 years old and about 63% of the patients had an ECOG-PS of 0.

Pembrolizumab (200 mg) was used in the intervention arm and placebo in the comparator arm in 21-day cycles. Treatment with pembrolizumab was limited to a maximum treatment

duration of 35 cycles (approximately 2 years), which deviates from the requirements in the product information, which stipulate therapy until cancer progression or until the occurrence of unacceptable toxicity. Chemotherapy was given in 28-day cycles on days 1, 8 and 15 in both the intervention and comparator arms. Paclitaxel was administered at a dose of 90 mg/m² BSA and nab-paclitaxel at a dose of 100 mg/m² BSA.

In the relevant sub-population, 49% of patients in the intervention arm received prior (neo)adjuvant chemotherapy and 45% in the control arm. The type of prior (neo)adjuvant chemotherapy was mostly comparable between treatment arms (taxane-containing 40% vs 32%; platinum-containing 7% vs 9%; anthracycline-containing 46% vs 40%).

The study population was treated until disease progression (determined by RECIST version 1.1 criteria), until the occurrence of unacceptable toxicity or intermediately occurring diseases requiring discontinuation of study medication, or until discontinuation of therapy by medical decision or patient choice. A changeover to the treatment of the other study arm was not planned.

The primary endpoints of the KEYNOTE 355 study are overall survival and progression-free survival. In addition, endpoints of the category's morbidity, health-related quality of life and adverse events are collected.

The study is being conducted in 251 study sites across Australia, Asia, Europe, New Zealand, and North and South America.

The results of the pre-specified final analysis of the KEYNOTE 355 study (data cut-off of 15 June 2021) are used for the benefit assessment.

Limitation of the KEYNOTE 355 study

The present marketing authorisation is based on the combination therapy of pembrolizumab with chemotherapy. The chemotherapy is not specified in more detail here and the approved therapeutic indication is also not restricted to the chemotherapeutic agents paclitaxel, nab-paclitaxel and gemcitabine/ carboplatin used in the KEYNOTE 355 study. [2]

In the dossier for the benefit assessment, the pharmaceutical company presents the pivotal KEYNOTE 355 study, in which pembrolizumab is being investigated in combination with nab-paclitaxel, paclitaxel or gemcitabine/ carboplatin.

A sub-population is considered, as the administration of therapies beyond the appropriate comparator therapy was also possible in the study. Due to the implementation of the appropriate comparator therapy, only the active ingredients nab-paclitaxel and paclitaxel are considered as chemotherapy in both the control and intervention arms. Therefore, no data are available for the combination of pembrolizumab with other approved chemotherapy concomitant active ingredients for the intervention arm.

Regarding the possibility of combination with chemotherapy, which is not specified, the EMA states as follows in the EPAR: " [...] Although not all drugs have been combined with pembrolizumab, and there are not necessarily safety data available for each combination, it is not expected that the benefit/risk balance will differ with other combinations, therefore, in line with EMA guidelines, the use of "chemotherapy" in SmPC 4.1 can be considered acceptable.[...]" With clinical studies that have shown a corresponding efficacy (KEYNOTE-

[2] Keytruda - European Public Assessement Report (EPAR) - EMEA/H/C/003820/II/0099; https://www.ema.europa.eu/documents/variation-report/keytruda-h-c-3820-ii-0099-epar-assessment-report-variation_en.pdf

522[3] and ENHANCE-1[4]), the EMA justifies the possibility of extrapolation to the combination of pembrolizumab with other chemotherapies used for the treatment of TNBC. In addition, the EMA states that no differences are to be expected between the various chemotherapeutic agents used in combination with pembrolizumab with regard to the benefit-risk assessment. The following possible chemotherapies are listed by the EMA based on current guidelines (ESMO ABC 5th[5]): Anthracyclines, taxanes, antimetabolites (capecitabine, gemcitabine), eribulin, platinum and combination chemotherapies for patients who have rapid clinical progression, life-threatening visceral metastases or an indication for rapid symptom and/or disease control.

In the written statement procedure, clinical experts point out that the combination therapy of pembrolizumab with anthracyclines has no significance in the care context. They point to missing study data. With regard to the combination of pembrolizumab with gemcitabine/ carboplatin, it is stated that this treatment option is relevant in the healthcare context.

Thus, the pharmaceutical company submitted data for the benefit assessment of pembrolizumab alone in combination with nab-paclitaxel or paclitaxel, but not in combination with another chemotherapy. In the present therapeutic indication, other chemotherapy agents are available that can be used in combination with chemotherapy according to the present marketing authorisation of pembrolizumab and are considered to be of relevant importance according to the current state of medical knowledge. In contrast to the question of the marketing authorisation, in which the benefit-risk ratio is assessed, the extent to which an extrapolation to further chemotherapy concomitant active ingredients could be made with regard to the present patient-relevant therapeutic effects must be assessed for the question of the benefit assessment.

Chemotherapy concomitant active ingredients can be pharmacologically very different chemotherapies and, in addition, variations in the treatment regime in relation to a particular chemotherapy. With regard to the effect in combination with pembrolizumab or with agents from the class of immune checkpoint inhibitors, only a certain selection of chemotherapy concomitant active ingredients has been investigated in phase 3 studies in the present therapeutic indication (paclitaxel, nab-paclitaxel, gemcitabine/ carboplatin).

There are no correspondingly significant data from the present benefit assessment procedure and also no findings according to the generally recognised state of medical knowledge that could lead to the assumption with sufficient certainty that the present results on patient-relevant therapeutic effects are transferable to other chemotherapy concomitant active ingredients.

In the present assessment of the G-BA, this leads to correspondingly different statements on the extent and probability of the additional benefit for pembrolizumab in combination with nab-paclitaxel or paclitaxel on the one hand, and for pembrolizumab in combination with a chemotherapy other than nab-paclitaxel or paclitaxel on the other.

Implementation of the appropriate comparator therapy:

The determination of the appropriate comparator therapy (anthracycline and/or taxane-containing systemic therapy) indicates that the marketing authorisation of the medicinal

[3]Pembrolizumab for Early Triple-Negative Breast Cancer; Peter Schmid et al.; N Engl J Med 2020; 382:810-821

[4]Eribulin Plus Pembrolizumab in Patients with Metastatic Triple-Negative Breast Cancer (ENHANCE 1): A Phase Ib/II Study; Tolaney et al.; Clin Cancer Res (2021) 27 (11): 3061–3068.

[5]Cardoso et al., 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020 Dec;31(12):1623-1649.

products must be taken into account. The active ingredient nab-paclitaxel from the taxane product class is not approved for the first-line treatment of locally advanced or metastatic breast cancer. In order to demonstrate that nab-paclitaxel is sufficiently comparable in therapeutic benefit to a taxane approved in the present therapeutic indication, the pharmaceutical company has presented data from various clinical studies in its dossier. These are, firstly, the studies by Luhn 2019 (Flatiron Health database), Gradishar 2005 (study CA0120-0) and Rugo 2015. In addition, the studies of Gradishar 2009 and Gradishar 2012 were presented.

These studies were already submitted in the benefit assessment procedure for atezolizumab in the same therapeutic indication and are assessed by the G-BA for the present assessment as follows.[6]

Of these studies submitted, the G-BA considers the publications by Gradishar 2009 and Gradishar 2012 to be particularly suitable. These are based on a phase II study in which patients with previously untreated metastatic breast cancer were randomised into the following study arms: 1. nab-paclitaxel 300mg/m² body surface area (BSA) every three weeks, 2. nab-paclitaxel 100mg/m² BSA weekly, 3. nab-paclitaxel 150mg/m² BSA weekly and 4. docetaxel 100mg/m² BSA every three weeks. Results on treatment response (progression-free survival and overall response rate) can be obtained from the publication Gradishar 2009. Data on overall survival were not yet available at this time; these were presented in the 2012 publication.

Although the statistical significance of this phase II study is limited, and the authors also point out that the results should be confirmed in a phase III study, the G-BA considers the study to be sufficiently suitable in terms of best available evidence to be able to be used for an assessment of comparability in the therapeutic benefit of nab-paclitaxel versus a taxane approved in the present therapeutic indication of pembrolizumab, in this case docetaxel. This assessment is made with regard to the question of whether the available data from the KEYNOTE 355 study on nab-paclitaxel can be suitable as a comparator for the assessment of the additional benefit of pembrolizumab in combination with nab-paclitaxel or paclitaxel.

In the KEYNOTE 355 study presented, both nab-paclitaxel and paclitaxel were used as comparators. Based on subgroup analyses according to the chemotherapy characteristic (paclitaxel vs nab-paclitaxel), it can be estimated that the results comparing pembrolizumab with nab-paclitaxel are sufficiently applicable to a comparison of pembrolizumab with paclitaxel.

In addition, the statements made by clinical experts in the present proceedings on this question are used for this assessment. Overall, these indicate the relevance of nab-paclitaxel in the present treatment setting. This is also reflected in current guidelines, including the German S3 guideline of the AWMF (Association of the Scientific-Medical Societies), in which nab-paclitaxel is either explicitly recommended or included in a recommendation for taxane therapy.

As a result, the G-BA comes to the conclusion that the data available from the KEYNOTE 355 study on nab-paclitaxel are sufficiently suitable as a comparator to enable an assessment of the additional benefit of pembrolizumab + nab-paclitaxel or paclitaxel.

Furthermore, there are uncertainties regarding the dosages of nab-paclitaxel or paclitaxel regularly used in the KEYNOTE 355 study.

[6] Gemeinsamer Bundesausschuss (Federal Joint Committee). Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Atezolizumab (New Therapeutic Indication: Breast Cancer from 2 April 2020.

With regard to the dosage of nab-paclitaxel, guidelines predominantly refer to a dosage of 125 mg/m² BSA weekly on days 1,8 and 15 of a 28-day cycle.

For paclitaxel, there is no specific information on the dosage of paclitaxel as first-line monotherapy in the product information. There is no consistent information in the guidelines. In the studies referenced in the guidelines, a dosing scheme of 175 mg/m² BSA paclitaxel every 3 weeks or 80 to 90 mg/m² BSA paclitaxel weekly was most commonly used. Based on the available information, the dosing scheme used in the KEYNOTE 355 study with 3 applications followed by a 1-week break does not appear appropriate and suggests undertreatment of patients in the comparator arm.

The statements made by clinical experts also critically discussed both the dosages used in the KEYNOTE 355 study and the treatment regimens of nab-paclitaxel or paclitaxel used. However, with regard to toxicities and associated therapy discontinuations, both a reduced dosage and weekly administration could be acceptable. However, the present study mainly enrolled patients who were in a good general condition according to ECOG performance status at the start of the study.

There are also uncertainties regarding the suitability of the patients included for treatment with paclitaxel. According to the inclusion criteria of the KEYNOTE 355 study, (neo)adjuvant therapy with anthracyclines had to have taken place, a contraindication to anthracyclines had to be present or anthracyclines did not represent the best treatment option in the opinion of the treating doctor. However, there are no data available to verify whether anthracyclines are actually no longer an option for any patient. Furthermore, based on the patient characteristics, it remains unclear to what extent a combination therapy containing anthracyclines and taxanes would also have been indicated for patients.

The G-BA considers the special therapy and medical treatment situation in the present therapeutic indication and the appraisal of the corresponding statements made by medical experts in the present procedure to be a sufficient medical reason that justifies the use of nab-paclitaxel as a sufficiently suitable comparator for the benefit assessment, despite remaining relevant uncertainties.

The G-BA points out that it will continue to adhere to the principles laid down in the provisions on benefit assessment according to Section 35a SGB V (AM-Nutzen and Chapter 5 of the G-BA's Rules of Procedure), thus also to the requirement laid down in Chapter 5, Section 6, para. 3, sentence 2 no. 1 VerfO that the comparator therapy in the clinical study used for the benefit assessment is used in conformity with the marketing authorisation.

Insofar as the nab-paclitaxel used as a comparator in this study was not used in conformity with the marketing authorisation, no conclusions can be derived from this regarding its appropriateness in the off-label form of application in the standard care of insured persons in the SHI system. Such an assessment would be reserved for the decision according to Section 35c SGB V.

Extent and probability of the additional benefit

a) Pembrolizumab in combination with nab-paclitaxel or paclitaxel

Mortality

Overall survival was operationalised in the KEYNOTE 355 study as the time from randomisation to death, regardless of the underlying cause.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of pembrolizumab in combination with nab-paclitaxel and or paclitaxel.

The extent of the prolongation achieved in overall survival is assessed as a significant improvement.

Morbidity

Progression-free survival (PFS)

PFS was operationalised in the KEYNOTE 355 study as the period from randomisation to the first documentation of disease progression or death from any cause, whichever occurs first. The evaluation was conducted by a blinded, independent, central review committee according to RECIST criteria (version 1.1).

There is a statistically significant prolonged PFS to the advantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. The endpoint component “mortality” is already surveyed in the present study via the endpoint “overall survival” as an independent endpoint. The morbidity component assessment was not done in a symptom-related manner but exclusively by means of imaging (disease progression assessed by radiology according to the RECIST 1.1 criteria). Taking into account the aspects mentioned above, there are different opinions within the G-BA regarding the patient relevance of the endpoint PFS. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology

Symptomatology was assessed in the KEYNOTE 355 study using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30 and the breast cancer-specific additional module QLQ-BR23.

The assessment of symptomatology was operationalised as time to first deterioration. Here, an increase in the score by ≥ 10 points compared to the start of the study was considered a clinically relevant deterioration.

Within the symptom scales of the EORTC QLQ-C30, there is a statistically significant difference to the disadvantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel for the diarrhoea scale.

Within the symptom scales of the EORTC QLQ-BR23, there is a statistically significant difference to the advantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel for the scale "Arm symptoms".

There was no statistically significant difference between treatment arms in health status, operationalised as time to first deterioration by ≥ 7 points and ≥ 10 points in the EQ-5D visual analogue scale (EQ-5D VAS).

In the overall assessment of the results, there is both an advantage and a disadvantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel compared to nab-paclitaxel or paclitaxel with regard to morbidity. Overall, there is no relevant difference.

Quality of life

Health-related quality of life was assessed in the KEYNOTE 355 study using the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires.

The assessment of quality of life was operationalised as time to first deterioration. Here, a decrease in the score by ≥ 10 points compared to the start of the study was considered a clinically relevant deterioration.

In the functional scales of the EORTC QLQ-C30 questionnaire, there is no statistically significant difference between the treatment arms.

There are also no statistically significant differences for the functional scales of the EORTC QLQ-BR23 questionnaire ("body image", "sexual activity" and "future perspective"). No usable data are available for the "sexual enjoyment" scale.

In terms of quality of life, there is thus no overall advantage or disadvantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel compared with nab-paclitaxel or paclitaxel.

Side effects

Adverse events (AEs) in total

In the KEYNOTE 355 study, AEs occurred in both study arms in almost all patients enrolled. The results were only presented additionally.

Serious adverse events (SAEs), severe adverse events (CTCAE grade ≥ 3) and discontinuation due to AEs

There is no statistically significant difference between the treatment arms for the endpoints SAEs, severe AEs and discontinuation due to AEs.

Specific adverse events

For the specific AE diarrhoea (PT, AEs), dysgeusia (PT, AEs) and gastrointestinal disorders (SOC, SAEs), there is a statistically significant difference to the disadvantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel in each case.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage can be found for pembrolizumab in combination with nab-paclitaxel or paclitaxel compared to nab-paclitaxel or paclitaxel. In detail, there are disadvantages in the specific AEs.

Overall assessment

For the benefit assessment of pembrolizumab in combination with nab-paclitaxel or paclitaxel for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 10) and who have not received prior chemotherapy for the treatment of metastatic disease, data on the relevant sub-population from the KEYNOTE 355 study on mortality, morbidity, quality of life and side effects are available.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of pembrolizumab in combination with nab-paclitaxel and or paclitaxel. The magnitude of the effect is assessed as a significant improvement.

In the morbidity category, there is a statistically significant difference to the disadvantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel within the symptom scales of the EORTC QLQ-C30 questionnaire for the diarrhoea scale. Within the symptom scales of the EORTC QLQ-BR23, there is a statistically significant difference to the advantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel for the scale "Arm

symptoms". In the overall assessment, no relevant difference is found with regard to morbidity.

In the functional scales of the EORTC QLQ-C30 and the EORTC QLQ-BR23 questionnaires ("body image", "sexual activity" and "future perspective"), there were no statistically significant differences between the treatment arms. No usable data are available for the "sexual enjoyment" scale. In terms of quality of life, no advantage or disadvantage of pembrolizumab in combination with nab-paclitaxel or paclitaxel can thus be determined overall.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage can be found for pembrolizumab in combination with nab-paclitaxel or paclitaxel compared to nab-paclitaxel or paclitaxel. In detail, there are disadvantages in the specific AEs.

Overall, there is a clear advantage in overall survival, no relevant differences in morbidity and quality of life, no relevant differences in overall rates in adverse events and in detail, disadvantages in specific adverse events. With regard to side effects, no relevant difference is found overall.

In the overall assessment, a quantifiability of the additional benefit is made in the present case, weighing up the uncertainties described and the magnitude of the effect in overall survival. Considerable additional benefit is identified for pembrolizumab in combination with nab-paclitaxel or paclitaxel in adults with locally recurrent unresectable or metastatic triple-negative breast cancer whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 10) and who have not received prior chemotherapy for the treatment of metastatic disease.

Reliability of data (probability of additional benefit)

The present KEYNOTE 355 study is a randomised, controlled, double-blind study.

The risk of bias of the result for the endpoint of overall survival is estimated to be low.

For the endpoints on symptomatology and health-related quality of life, the risk of bias of the results is assessed as high in each case, as there was a strongly decreasing response to the respective questionnaires in both treatment arms and a strongly differentiated response between the treatment arms.

Furthermore, there are uncertainties regarding the dosages of the comparators nab-paclitaxel or paclitaxel that were regularly used in the KEYNOTE 355 study. The statements made by clinical experts also critically discussed both the dosages used in the KEYNOTE 355 study and the treatment regimens of nab-paclitaxel and paclitaxel used. However, with regard to toxicities and associated therapy discontinuations, both a reduced dosage and 3-weekly administration followed by a 1-week break in therapy could be acceptable.

Further uncertainty exists with regard to the question to what extent or for what percentage of the patients enrolled in the KEYNOTE 355 study an anthracycline-containing combination therapy could also be considered in the reality of care.

Consequently, in the overall assessment, the reliability of data of the additional benefit identified is classified as a hint.

b) Pembrolizumab in combination with chemotherapy other than nab-paclitaxel or paclitaxel

No data are available to allow an assessment of the additional benefit.

2.1.4 Summary of the assessment

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

"Keytruda, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for the treatment of metastatic disease."

The assessment is based on the KEYNOTE 355 study, which investigated pembrolizumab in combination with paclitaxel or nab-paclitaxel or gemcitabine/ carboplatin in comparison with paclitaxel or nab-paclitaxel or gemcitabine/ carboplatin. The assessment is based on evaluations of a sub-population of patients with tumours that express PD-L1 (CPS ≥ 10) according to the marketing authorisation and allocation to taxane chemotherapy (paclitaxel or nab-paclitaxel) before randomisation.

As the assessment only has data for pembrolizumab in combination with nab-paclitaxel or paclitaxel, but not in combination with another chemotherapy, separate statements on the additional benefit are made in this regard:

a) Pembrolizumab in combination with nab-paclitaxel or paclitaxel

b) Pembrolizumab in combination with chemotherapy other than nab-paclitaxel or paclitaxel

Assessment of the additional benefit for a)

For the evaluation, results on overall survival, morbidity, quality of life and side effects are available.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of pembrolizumab in combination with nab-paclitaxel and or paclitaxel. The magnitude of the effect is assessed as a significant improvement.

In the endpoint categories of morbidity and health-related quality of life, there are no relevant differences overall.

In the overall assessment of the results on side effects, neither an advantage nor a disadvantage can be found for pembrolizumab in combination with nab-paclitaxel or paclitaxel compared to nab-paclitaxel or paclitaxel.

As a result, the G-BA found a considerable additional benefit.

The reliability of data of the additional benefit identified is classified as a hint.

Assessment of the additional benefit for b)

No data are available to allow an assessment of the additional benefit. An additional benefit is not proven.

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. However, the following uncertainties arise, which lead to an overall underestimation:

Compared to the incidence rates predicted by the Robert Koch Institute and Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (Association of Population Based Cancer Registries in Germany), the pharmaceutical company assumes lower incidence rates for breast cancer in women.

With regard to the stage distribution, there are uncertainties for the percentage values for patients with breast cancer with unknown stage or in stage IV at first diagnosis. In addition, patients with stage IIIC breast cancer at initial diagnosis who are not included in the present therapeutic indication according to the product information are included.

Underestimates also result from the lack of consideration of patients who were first diagnosed before 2020 and who progress to stage IV in the year under review, as well as patients who were first diagnosed in 2020 or earlier and who show an unresectable local relapse for the first time in the year under review or who progress from stage IIIC to stage IV.

Uncertainties also exist with regard to the percentage value of TNBC.

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: 17 March 2022):

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 as well as specialists in obstetrics and gynaecology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of adults with breast cancer.

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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2022).

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

The treatment regimens doxorubicin + cyclophosphamide, doxorubicin + docetaxel, epirubicin + cyclophosphamide, epirubicin + docetaxel and epirubicin + paclitaxel were based on the treatment modes of the German S3 guideline (version 4.4).[7]

For doxorubicin and epirubicin, the cumulative total dose was considered (450 - 550 mg/m² for doxorubicin and 900 - 1,000 mg/m² for epirubicin). Product information with different dosage recommendations is available for doxorubicin and epirubicin (doxorubicin: 50 - 80 mg/m² and 60 - 75 mg/m²; epirubicin: 75 - 90 mg/m² and 60 - 90 mg/m². The dosage recommendations with the largest range were used for the cost calculation: Doxorubicin 50 - 80 mg/m² and epirubicin: 60 - 90 mg/m².

The average body measurements of adult females were applied for dosages, depending on body weight (BW) or body surface area (BSA) (average body height: 1,66 m; average body weight: 68.7 kg).[8] This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916).

Chemotherapy component in combination with pembrolizumab

The marketing authorisation of pembrolizumab in combination with chemotherapy is not restrictive with regard to the chemotherapy component. Explanatory comments in this regard are set out in the European Medicines Agency (EMA) assessment report (EPAR).[2]

Thus, a variety of different chemotherapies and treatment regimens may be considered with respect to the chemotherapy component. Therefore, the treatment costs for "b) Pembrolizumab in combination with chemotherapy other than nab-paclitaxel or paclitaxel" are reported as not determinable.

[7] Guidelines Programme Oncology (ed.): Interdisciplinary S3 guideline for early detection, diagnosis, therapy and follow-up of breast cancer, 2021. https://www.leitlinienproGramm-onkologie.de/leitlinien/mammakarzinom/

[8] Federal Health Reporting. Average body measurements of the population (2017), www.gbe-bund.de

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				
Pembrolizumab	1 x every 21 days	17.4	1	17.4
	or			
	1 x every 42 days	8.7	1	8.7
in combination with				
nab-paclitaxel	on day 1, 8 and 15 of 28-day cycle	13.0	3.0	39.0
or				
Paclitaxel	on day 1, 8 and 15 of 28-day cycle	13.0	3.0	39.0
or				
chemotherapy other than nab-paclitaxel or paclitaxel	Not determinable			
Appropriate comparator therapy				
Anthracycline and/or taxane-containing therapy				
Docetaxel				
Docetaxel	1 x every 21 days	17.4	1	17.4
Docetaxel + capecitabine				
Docetaxel	1 x every 21 days	17.4	1	17.4
Capecitabine	2 x daily on day 1-14 of a 21-day cycle	17.4	14	243.6
Doxorubicin				
Doxorubicin	1 x every 21 days	5 - 11[9]	1	5 - 11
Doxorubicin + docetaxel				
Doxorubicin	1 x every 21 days	9 - 11[4]	1	9 - 11
Docetaxel	1 x every 21 days	17.4	1	17.4

[9] Based on total cumulative dose of maximum 450 - 550 mg/m².

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Doxorubicin + cyclophosphamide				
Doxorubicin	1 x every 21 days	7 - 9[4]	1	7 - 9
Cyclophosphamide	1 x every 21 days	17.4	1	17.4
Doxorubicin + paclitaxel				
Doxorubicin	1 x every 21 days	9 - 11[4]	1	9 - 11
Paclitaxel	1 x every 21 days	17.4	1	17.4
Doxorubicin pegylated, liposomal				
Doxorubicin pegylated, liposomal	1 x every 28 days	13	1	13
Liposomal doxorubicin + cyclophosphamide				
Liposomal doxorubicin	1 x every 21 days	17.4	1	17.4
Cyclophosphamide	1 x every 21 days	17.4	1	17.4
Epirubicin				
Epirubicin	1 x every 21 days	10 - 16[10]	1	10 - 16
Epirubicin + cyclophosphamide				
Epirubicin	1 x every 21 days	13 -15[5]	1	13 - 15
Cyclophosphamide	1 x every 21 days	17.4	1	17.4
Epirubicin + docetaxel				
Epirubicin	1 x every 21 days	12 - 13[5]	1	12 - 13
Docetaxel	1 x every 21 days	17.4	1	17.4
Epirubicin + paclitaxel				
Epirubicin	1 x every 21 days	15 - 16[5]	1	15 - 16
Paclitaxel	1 x every 21 days	17.4	1	17.4
Paclitaxel				
Paclitaxel	1 x every 21 days	17.4	1	17.4
Gemcitabine + paclitaxel				
Gemcitabine	on day 1 and 8 of a 21-day cycle	17.4	2	34.8
Paclitaxel	1 x every 21 days	17.4	1	17.4

[10] Based on total cumulative dose of maximum 900 - 1,000 mg/m².

Consumption:

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					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17.4	34.8 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8.7	34.8 x 100 mg
in combination with					
nab-paclitaxel	100 mg/m^2 = 176 mg	176 mg	2 x 100 mg	39	78 x 100 mg
or					
Paclitaxel	90 mg/m^2 = 158.4 mg	158.4 mg	1 x 100 mg + 2 x 30 mg	39	39 x 100 mg + 78 x 30 mg
or					
chemotherapy other than nab-paclitaxel or paclitaxel	Not determinable				
Appropriate comparator therapy					
Anthracycline and/or taxane-containing therapy					
Docetaxel					
Docetaxel	100 mg/m^2 = 176 mg	176 mg	1 x 140 mg + 2 x 20 mg	17.4	17.4 x 140 mg + 34.8 x 20 mg
Docetaxel + capecitabine					
Docetaxel	75 mg/m^2 = 132 mg	132 mg	1 x 140 mg	17.4	17.4 x 140 mg
Capecitabine	1,250 mg/m^2 = 2200 mg	2 x 2200 = 4400 mg	8 x 500 mg + 4 x 150 mg	243.6	1948.8 x 500 mg + 974.4 x 150 mg
Doxorubicin					
Doxorubicin	80 mg/m^2 = 140.8 mg	140.8 mg -	1 x 150 mg -	5 -	5 x 150 mg -

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	- 50 mg/m² = 88 mg	88 mg	1 x 100 mg	11	11 x 100 mg
Doxorubicin + docetaxel					
Doxorubicin	50 mg/m² = 88 mg	88 mg	1 x 100 mg	9 - 11	9 x 100 mg - 11 x 100 mg
Docetaxel	75 mg/m² = 132 mg	132 mg	1 x 140 mg	17.4	17.4 x 140 mg
Doxorubicin + cyclophosphamide					
Doxorubicin	60 mg/m² = 105.6 mg	105.6 mg	1 x 100 mg + 1 x 10 mg	7 - 9	7 x 100 mg + 7 x 10 mg - 9 x 100 mg + 9 x 10 mg
Cyclo-phosphamide	600 mg/m² = 1056 mg	1056 mg	1 x 1,000 mg + 1 x 200 mg	17.4	17.4 x 1,000 mg + 17.4 x 200 mg
Doxorubicin + paclitaxel					
Doxorubicin	50 mg/m² = 88 mg	88 mg -	1 x 100 mg	9 - 11	9 x 100 mg - 11 x 100 mg
Paclitaxel	220 mg/m² = 387.2 mg	387.2 mg	1 x 300 mg + 1 x 100 mg	17.4	17.4 x 300 mg + 17.4 x 100 mg
Doxorubicin pegylated, liposomal					
Doxorubicin pegylated, liposomal	50 mg/m² = 88 mg	88 mg	2 x 20 mg + 1 x 50 mg	13	26 x 20 mg + 13 x 50 mg
Liposomal doxorubicin + cyclophosphamide					
Liposomal doxorubicin	60 mg/m2 = 105.6 mg - 75 mg/m2 = 132 mg	105.6 mg - 132 mg	3 x 50 mg	17.4	52.2 x 50 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Cyclo-phosphamide	600 mg/m2 = 1056 mg	1056 mg	1 x 1,000 mg + 1 x 200 mg	17.4	17.4 x 1,000 mg + 17.4 x 200 mg
Epirubicin					
Epirubicin	90 mg/m^2 = 158.4 mg - 60 mg/m^2 = 105.6 mg	158.4 mg - 105.6 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg - 1 x 100 mg + 1 x 10 mg	10 - 16	10 x 100 mg + 10 x 50 mg + 10 x 10 mg - 16 x 100 mg + 16 x 10 mg
Epirubicin + cyclophosphamide					
Epirubicin	75 mg/m^2 = 132 mg - 60 mg/m^2 = 105.6 mg	132 mg - 105.6 mg	1 x 100 mg + 1 x 50 mg - 1 x 100 mg + 1 x 10 mg	13 - 15	13 x 100 mg + 13 x 50 mg - 15 x 100 mg + 15 x 10 mg
Cyclo-phosphamide	600 mg/m^2 = 1056 mg	1056 mg	1 x 1,000 mg + 1 x 200 mg	17.4	17.4 x 1,000 mg + 17.4 x 200 mg
Epirubicin + docetaxel					
Epirubicin	75 mg/m^2 = 132 mg	132 mg	1 x 100 mg + 1 x 50 mg	12 - 13	12 x 100 mg + 12 x 50 mg - 13 x 100 mg + 13 x 50 mg
Docetaxel	75 mg/m^2 = 132 mg	132 mg	1 x 140 mg	17.4	17.4 x 140 mg
Epirubicin + paclitaxel					
Epirubicin	60 mg/m^2 = 105.6 mg	105.6 mg	1 x 100 mg + 1 x 10 mg	15 - 16	15 x 100 mg + 15 x 10 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					- 16 x 100 mg + 16 x 10 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Paclitaxel					
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg
Gemcitabine + paclitaxel					
Gemcitabine	1250 mg/m² = 2200 mg	2200 mg	1 x 2200 mg	34.8	34.8 x 2200 mg
Paclitaxel	175 mg/m² = 308 mg	308 mg	1 x 300 mg + 1 x 30 mg	17.4	17.4 x 300 mg + 17.4 x 30 mg

Costs:

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 in combination with chemotherapy					
Pembrolizumab 100 mg	1 CIS	€ 3,037.30	€ 1.77	€ 170.17	€ 2,865.36
nab-paclitaxel 100 mg	1 PIS	€ 429.33	€ 1.77	€ 52.91	€ 374.65
Paclitaxel 30 mg	1 CIS	€ 115.75	€ 1.77	€ 4.96	€ 109.02

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
Paclitaxel 100 mg	1 CIS	€ 304.03	€ 1.77	€ 13.89	€ 288.37
Appropriate comparator therapy					
Capecitabine 150 mg[11]	120 FCT	€ 54.11	€ 1.77	€ 3.39	€ 48.95
Capecitabine 500 mg[6]	120 FCT	€ 151.81	€ 1.77	€ 11.12	€ 138.93
Cyclophosphamide 200 mg	10 PSI	€ 61.21	€ 1.77	€ 2.77	€ 56.67
Cyclophosphamide 1000 mg	6 PSI	€ 123.94	€ 1.77	€ 6.24	€ 115.93
Docetaxel 20 mg	1 CIS	€ 112.43	€ 1.77	€ 4.80	€ 105.86
Docetaxel 140 mg	1 CIS	€ 719.30	€ 1.77	€ 33.60	€ 683.93
Doxorubicin 10 mg[6]	1 CIS	€ 40.28	€ 1.77	€ 2.29	€ 36.22
Doxorubicin 100 mg[6]	1 CIS	€ 285.75	€ 1.77	€ 0.00	€ 283.98
Doxorubicin 150 mg[6]	1 SFI	€ 418.32	€ 1.77	€ 0.00	€ 416.55
Doxorubicin, liposomal 50 mg	1 DSS	€ 1,251.19	€ 1.77	€ 68.65	€ 1,180.77
Doxorubicin, PEG-liposomal 20 mg	1 CIS	€ 776.63	€ 1.77	€ 42.37	€ 732.49
Doxorubicin, PEG-liposomal 50 mg	1 CIS	€ 1,912.60	€ 1.77	€ 105.94	€ 1,804.89
Epirubicin hydrochloride 10 mg	1 CIS	€ 39.47	€ 1.77	€ 1.34	€ 36.36
Epirubicin hydrochloride 50 mg	1 CIS	€ 155.41	€ 1.77	€ 6.84	€ 146.80
Epirubicin hydrochloride 100 mg	1 CIS	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Gemcitabine 2200 mg	1 INF	€ 495.80	€ 1.77	€ 22.99	€ 471.04
Paclitaxel 100 mg	1 CIS	€ 304.03	€ 1.77	€ 13.89	€ 288.37
Paclitaxel 300 mg	1 CIS	€ 891.24	€ 1.77	€ 41.76	€ 847.71
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; INF = infusion solution; PIS = powder for the preparation of an infusion suspension; PSI = powder for solution for injection; DSS = dry substance with solvent					

LAUER-TAXE® last revised: 15 April 2022

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.

[11] Fixed reimbursement rate

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							
Paclitaxel							
Dexamethasone 20 mg	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	17.4	€ 81.49
Dimetindene IV 1 mg/10 kg	5 x 4 mg SFI	€ 18.86	€ 1.77	€ 1.90	€ 15.19	17.4	€ 105.72
Cimetidine IV 300 mg	10 AMP each 200 mg	€ 21.79	€ 1.77	€ 0.00	€ 19.19	17.4	€ 69.67
Appropriate comparator therapy							
Paclitaxel							
Dexamethasone 20 mg	50 TAB	€ 118.85	€ 1.77	€ 0.00	€ 117.08	17.4	€ 81.49
Dimetindene IV 1 mg/10 kg	5 x 4 mg SFI	€ 18.86	€ 1.77	€ 1.90	€ 15.19	17.4	€ 105.72
Cimetidine IV 300 mg	10 AMP each 200 mg	€ 21.79	€ 1.77	€ 0.00	€ 19.19	17.4	€ 69.67
Abbreviations: SFI = solution for injection; TAB = tablets; AMP = ampoules							

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

3. Bureaucratic costs calculation

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

4. Process sequence

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

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 20 October 2021.

On 12 November 2021, 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.

By letter dated 16 November 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 February 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 February 2022. The deadline for submitting written statements was 9 March 2022.

The oral hearing was held on 28 March 2022.

By letter dated 29 March 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 14 April 2022.

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 26 April 2022, and the proposed resolution was approved.

At its session on 5 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 December 2019	Determination of the appropriate comparator therapy
Subcommittee	20 October 2021	New determination of the appropriate comparator therapy

Medicinal products		
Working group Section 35a	23 March 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	28 March 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	6 April 2022 20 April 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	26 April 2022	Concluding discussion of the draft resolution
Plenum	5 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 May 2022

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

Prof. Hecken