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, high risk of recurrence, neoadjuvant and adjuvant therapy, monotherapy or combination with chemotherapy)

of 15 December 2022

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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 May 2022, 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 16 June 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new

therapeutic indication (Keytruda, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 4 October 2022 on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

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

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

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

2.1.1 Approved therapeutic indication of Pembrolizumab (Keytruda) in accordance with the product information

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence.

Therapeutic indication of the resolution (resolution of 15 December 2022):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence; neoadjuvant and adjuvant therapy

Appropriate comparator therapy:

Chemotherapy according to doctor's instructions for neoadjuvant treatment followed by monitoring wait-and-see approach after surgery

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

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-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. For the present therapeutic indication, the active ingredients doxorubicin, epirubicin, mitoxantrone and vincristine are approved for neoadjuvant treatment in addition to pembrolizumab. In addition to pembrolizumab, the following active ingredients are approved for adjuvant treatment: cyclophosphamide, docetaxel, doxorubicin, epirubicin, fluorouracil, methotrexate, paclitaxel, vincristine and olaparib.

On 2. In the present therapeutic indication, a radiotherapy is considered as non-medicinal treatment.

On 3. For the planned therapeutic indication there are the following resolutions or guidelines of the G-BA for medicinal applications or non-medicinal treatments.

Directive on Examination and Treatment Methods in Hospitals (Directive on Methods of Inpatient Treatment) - Methods excluded from provision at the expense of the statutory health insurance funds; entered into force on 20 March 2019:

- Proton therapy for breast cancer

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

- Gemcitabine in monotherapy for breast cancer in women

There are no resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication. 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.

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

According to the current S3 guideline, chemotherapy can be given before surgery (neoadjuvant) or thereafter (adjuvant), if indicated. Here, neoadjuvant treatment is preferably recommended, provided that the same systemic chemotherapy is considered both adjuvant and neoadjuvant. For neoadjuvant treatment of breast cancer, the same chemotherapy combinations as for adjuvant treatment are generally recommended according to current guidelines.

For the adjuvant treatment of breast cancer, this is by default a taxane and anthracycline-based chemotherapy. This can be done in sequence or combination. Meta-analyses have shown that the addition of taxane-based chemotherapy to standard anthracycline-based treatment improves overall survival (OS) and disease-free survival (DFS). For anthracycline-containing chemotherapy protocols, cardiac risks should be considered in the treatment decision.

The active ingredients paclitaxel and cyclophosphamide are approved for adjuvant therapy, but not explicitly for the neoadjuvant treatment setting, but are also recommended in guidelines for neoadjuvant therapy. Thus, there is a discrepancy between medicinal therapies approved in the indication and those recommended by guidelines or used in care.

Against this background, for neoadjuvant treatment, the G-BA determines chemotherapy as an appropriate comparator therapy according to doctor's instructions, for which a sequential or combined chemotherapy regimen containing a taxane and an anthracycline is determined as an appropriate comparator.

Furthermore, the guidelines recommend a weekly paclitaxel dosage of 80 mg/m^2 which, however, differs from the information given in the product information of paclitaxel (administration of 175 mg/m^2 once every three weeks).

The active ingredient carboplatin is not approved in the present therapeutic indication for either the adjuvant or the neoadjuvant treatment setting. In addition, there is no higher-quality evidence for treatment with carboplatin in the present therapeutic indication.

The active ingredient olaparib from the product class of PARP inhibitors is a new treatment option for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative early-stage breast cancer at high risk of recurrence and who were pretreated with neoadjuvant or adjuvant chemotherapy. The active ingredient olaparib is a new treatment option in the present therapeutic indication. The active ingredient was only recently approved (marketing authorisation on

02.08.2022). Based on the generally accepted state of medical knowledge, olaparib is not determined to be an appropriate comparator therapy for the present resolution.

Provided that the taxane and anthracycline-based chemotherapy has already taken place in the neoadjuvant treatment setting, there is no recommendation according to the guidelines for further, regular antineoplastic therapy in the postoperative, adjuvant treatment setting. Therefore, monitoring wait-and-see approach is determined as the comparator therapy for adjuvant treatment in the present therapeutic indication.

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

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

2.1.3 Extent and probability of the additional benefit

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

a) Pembrolizumab in combination with paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

There is a hint for a minor additional benefit of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab monotherapy (adjuvant) for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence.

b) Pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin, followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

An additional benefit is not proven for pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin, followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence.

Justification:

For the evidence of an additional benefit, the pharmaceutical company submitted the results of the still ongoing, double-blind, randomised, controlled KEYNOTE 522 study in the dossier, in which pembrolizumab in combination with chemotherapy for neoadjuvant and then after surgery as monotherapy for adjuvant treatment is compared to placebo in combination with

chemotherapy for neoadjuvant treatment and then after surgery to placebo for adjuvant treatment.

The study enrolled adult patients with locally advanced, or early-stage non-metastatic triple-negative breast cancer (TNBC) at high risk of recurrence who had not received prior treatment at this stage of TNBC. A total of 1,174 patients were enrolled in the study and randomised in a 2:1 ratio to either treatment with pembrolizumab + chemotherapy (neoadjuvant), followed by pembrolizumab (adjuvant) (N = 784) or to treatment with placebo + chemotherapy (neoadjuvant), followed by placebo (adjuvant) (N = 390). Randomisation was stratified by nodal status (positive vs negative), tumour size (T1/T2 vs T3/T4) and carboplatin therapy regimen (every 3 weeks vs once weekly).

Due to the implementation of the appropriate comparator therapy, only the active ingredients paclitaxel and carboplatin, followed by doxorubicin or epirubicin and cyclophosphamide are considered as neoadjuvant chemotherapy in both the control and intervention arms. Therefore, no data are available for the combination of pembrolizumab with other chemotherapy concomitant active ingredients for the intervention arm.

The neoadjuvant treatment with pembrolizumab in combination with chemotherapy, followed by adjuvant treatment with pembrolizumab as monotherapy in the intervention arm complied with the requirements in the product information. Neoadjuvant treatment with chemotherapy in both study arms was initially 4 cycles of 3 weeks each with paclitaxel + carboplatin, followed by a further 4 cycles of 3 weeks each with doxorubicin or epirubicin + cyclophosphamide.

While it can be assumed for the intervention arm of the KEYNOTE 522 study that the therapy of pembrolizumab in combination with chemotherapy given in the neoadjuvant phase in this arm is approved overall due to the marketing authorisation of pembrolizumab, this does not apply to the control arm. The chemotherapy regimen given in the control arm contained carboplatin which is not approved in the present indication. In addition, other active ingredients were used in chemotherapy that are not explicitly approved for neoadjuvant treatment.

The currently ongoing KEYNOTE 522 study is being conducted at 177 study sites in Asia, Australia, Europe, North America and South America. Co-primary endpoints of the KEYNOTE 522 study are pathological complete remission (pCR) and event-free survival (EFS). Patient-relevant secondary endpoints include endpoints of the categories mortality, morbidity, health-related quality of life, and adverse events (AEs).

<u>On the usability of the study results presented in the dossier</u>

At the time of the benefit assessment, a total of 5 pre-specified data cut-offs are available. In the dossier, the pharmaceutical company presented the results on the 4th data cut-off from 23.03.2021. From a separate document provided by the pharmaceutical company as a note to the study report of the 4th data cut-off, it is clear that the null hypothesis for event-free survival (EFS) could be rejected as early as the 4th data cut-off and therefore the primary goal was the evaluation of overall survival as of the 5th data cut-off - contrary to the original plan.

However, for the 5th data cut-off from 23.03.2022, the pharmaceutical company did not submit any evaluations in the dossier. As justification, it states that it was not fallen below the

significance threshold for overall survival. According to the separate note to the study report, an external Data Monitoring Committee (eDMC) has reviewed the results of the 5th data cut-off on efficacy and safety on 23.05.2022. The eDMC recommended that the study be continued as a blinded one until the null hypothesis for overall survival could be rejected.

IQWiG assessed the decision not to present the results of the 5th data cut-off to be inappropriate. The justification given by the pharmaceutical company for not reaching the significance threshold for the endpoint of overall survival in the 5th data cut-off is not well-founded. The point mentioned in the note to the study report to continue the study as a blinded one was also not understandable, as there were already published evaluations for all endpoints, i.e. also for overall survival, for the previous 4th data cut-off.

In principle, according to the dossier template, complete evaluations for all patient-relevant endpoints collected are to be conducted and submitted for all of the data cut-offs relevant for the benefit assessment. According to IQWiG, such evaluations are already available for the 5th data cut-off according to the information in the separate note document. As a result, IQWiG assessed the pharmaceutical company's dossier as incomplete in terms of content, but used the results of the 4th data cut-off, since the 5th data cut-off yielding relevantly different results is not assumed in the present data situation.

The G-BA is critical of the pharmaceutical company's approach. However, since no relevantly different results are expected for the 5th data cut-off compared to the 4th data cut-off according to IQWiG, and since it can be assumed that the overall survival does not fall below the significance threshold, the results of the 4th data cut-off from 23.03.2021 are still used for the present benefit assessment.

Limitation of the KEYNOTE 522 study

The present marketing authorisation is based on the neoadjuvant combination therapy of pembrolizumab with a chemotherapy. The chemotherapy is not specified in more detail here and the approved therapeutic indication is also not restricted to the chemotherapeutic agents paclitaxel and carboplatin, followed by doxorubicin or epirubicin and cyclophosphamide used in the KEYNOTE 522 study.

In the dossier for the benefit assessment, the pharmaceutical company presents the KEYNOTE 522 pivotal study, in which pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and monotherapy with pembrolizumab (adjuvant) is investigated. Other chemotherapy concomitant active ingredients are not being investigated in the study.

Regarding the possibility of combination with chemotherapy other than that used in the KEYNOTE 522 study, the EMA states in the EPAR that an anthracycline-based regimen followed by a taxane-based regimen is the preferred therapy in the therapeutic indication and that the use of carboplatin is a treatment option for the treatment of triple-negative breast cancer. However, other possible chemotherapy concomitant active ingredients specifically for treatment with pembrolizumab are not named in the EPAR.

Within the framework of the written statement procedure, the clinical assessment experts also explained that the chemotherapy combination used in the study is a treatment standard in the therapeutic indication. With regard to other possible chemotherapy concomitant active ingredients, no further active ingredients were named.

Thus, data were submitted by the pharmaceutical company for the benefit assessment of pembrolizumab in combination with paclitaxel and carboplatin alone, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant). However, the wording of the therapeutic indication does not exclude the use of pembrolizumab in combination with other chemotherapy options. In addition to the anthracycline and taxane-based chemotherapy regimen used by the pharmaceutical company in the study, other anthracycline and/or taxane-based chemotherapy regimens are recommended in the guidelines.

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.

Variations in the treatment regimen in relation to chemotherapy may also be considered. With regard to the effect in combination with pembrolizumab or with active ingredients 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 and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide).

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 additional benefit of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) on the one hand, and of pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin, followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) on the other.

Implementation of the appropriate comparator therapy

The active ingredient carboplatin is not approved in the present therapeutic indication for either the adjuvant or the neoadjuvant treatment setting. The use of carboplatin is controversially discussed by the European Medicines Agency (EMA) and in the guidelines, as carboplatin administration has been shown to increase the rate of pathological complete remissions (pCR), but without a consistent improvement in overall survival and at the cost of worse haematological toxicity.

Within the framework of the written statement procedure, the clinical experts explained that the use of carboplatin has a clear added value for the patients from a clinical point of view and represents the therapy standard, especially in the curative setting of the younger high-risk group.

The active ingredient paclitaxel is only approved for the adjuvant treatment setting. In addition, there is uncertainty about the dosage and frequency of administration of paclitaxel:

The dosage of 80 mg/m² body surface area (BSA) used in the study with weekly administration differs from the dosage of 175 mg/m² BSA every 3 weeks shown in the product information.

With regard to the administration of paclitaxel in the neoadjuvant treatment setting, the guidelines recommend that any postoperative adjuvant therapy indicated should preferably be administered as neoadjuvant therapy. The guidelines do not include any uniform recommendations on the dosage used.

In this regard, the clinical experts stated during the written statement procedure that weekly administration at a lower dosage is the current treatment standard, as the effectiveness is somewhat higher than with administration once every three weeks.

Overall, the clinical assessment experts point out that the chemotherapy combination used in the study represents a therapy standard in the therapeutic indication.

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 carboplatin and paclitaxel as sufficiently suitable comparators 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 active ingredients carboplatin and paclitaxel used as comparators in this study were not used in conformity with the marketing authorisation, no conclusions can be derived from this regarding their 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 paclitaxel and carboplatin followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

Mortality

Overall survival was defined in the KEYNOTE 522 study as the time from randomisation to death, regardless of the underlying cause.

For the endpoint of overall survival, no statistically significant difference was detected between the treatment groups. At the time of the 4th data cut-off, 80 patients (10.2%) in the intervention arm and 55 patients (14.1%) in the comparator arm had died.

Morbidity

Recurrences (recurrence rate and event-free survival)

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

The significance of the 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.

In the present benefit assessment, recurrences are taken into account in the endpoint of recurrence rate as well as in the endpoint of event-free survival. Both evaluations include the following events:

- Local progression preventing definitive surgery
- Local progression preventing surgery
- Positive resection margin in the last surgery
- Local recurrence
- Remote recurrence
- Remote metastases
- Second primary tumour
- Death, regardless of cause

In the present therapeutic indication, this operationalisation is suitable to depict a failure of the potential cure by the curative therapeutic approach.

There is a statistically significant difference in both recurrence rate and event-free survival to the advantage of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) compared to the appropriate comparator therapy.

When considering both endpoints, an overall relevant advantage with regard to the avoidance of recurrences is observed for pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant).

Pathological complete remission (pCR)

The endpoint of pathological complete remission (ypT0/Tis ypN0) is one of the two co-primary endpoints in the KEYNOTE 522 study and was defined in the study as the percentage of patients in whom no invasive tumour cells are detected in the resectate from the breast and regional lymph nodes.

For the endpoint of pathological complete remission, there is a statistically significant difference in favour of pembrolizumab in combination with chemotherapy (neoadjuvant), followed by pembrolizumab (adjuvant) compared to the appropriate comparator therapy.

Although it is clear from the S3 guideline as well as from the statements of clinical experts that a very favourable long-term prognosis can be assumed in the case of pathological complete remission, there are so far no reliable data at study level that show that differences with regard to the pCR rate between the study arms also reliably predict differences with regard to event-free survival or overall survival. Overall, pCR is currently not a valid surrogate endpoint for patient-relevant endpoints. The pharmaceutical company also did not provide evidence for a validation of the surrogate endpoint in the dossier.

Therefore, the results are only presented additionally.

Breast-conserving surgery (BCS)

The endpoint of breast-conserving surgery (BCS) is defined in the KEYNOTE 522 study as the rate of those patients who were able to undergo breast-conserving surgery.

For the endpoint of breast-conserving surgery, no statistically significant difference was detected between the treatment arms.

Symptomatology and health status

In the KEYNOTE 522 study, the endpoint of symptomatology was assessed using the EORTC QLQ-C30 and the EORTC QLQ-BR23. Health status was assessed in the KEYNOTE 522 study using the EQ-5D visual analogue scale (VAS).

In the dossier, the pharmaceutical company presented separate analyses using constrained longitudinal data analysis (cLDA) for the neoadjuvant and adjuvant treatment phases and presented the results of the change from baseline of the respective treatment phase as well as the mean differences between the study arms. In addition, the scores for each scale were reported descriptively for specific time points in the course of the study. The pharmaceutical company had not submitted evaluations of the entire course of the study. However, the separate evaluation of the neoadjuvant and adjuvant treatment phases is not appropriate, as only a greatly reduced percentage of patients in the ITT population, which differed between the treatment arms, was included in the evaluation of the adjuvant treatment phase. This percentage represents a sub-population selected by the neoadjuvant treatment, so that a randomised comparison can no longer be assumed. A sole consideration of the neoadjuvant treatment phase is not considered meaningful for the derivation of the additional benefit, as no statement about the overall treatment period approved is possible.

Within the framework of the written statement procedure, the pharmaceutical company submitted evaluations by means of constrained Longitudinal Data Analysis (cLDA) over both treatment phases of the KEYNOTE 522 study.

The analyses presented cover the comparison from the start of the neoadjuvant treatment phase to week 24 of the adjuvant treatment phase. Therefore, from the data presented, statements can only be made about a treatment duration of approx. 1 year and not about the entire course of the study up to 2 years after randomisation.

In IQWiG's view, the data presented are not interpretable. The reason for this are the overall strongly decreasing return rates of the questionnaires in the course of observation (at week 24 of the adjuvant treatment phase only approx. 57% in the intervention arm and 64% in the control arm). The drop in return rates between the last visit under neoadjuvant treatment (approx. 79% in the intervention arm and 81% in the control arm) and the first visit under adjuvant treatment (approx. 64% in the intervention arm and 74% in the control arm) is of particular relevance.

Thus, no assessable data are available overall for the endpoints of symptomatology and health status.

In summary, in the endpoint category of morbidity, there is an advantage of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) with regard to the prevention of recurrences. Regarding the endpoint of breast-conserving surgery (BCS), there were no statistically significant differences between the

treatment groups. No assessable data are available for the endpoints of symptomatology and health status.

Quality of life

EORTC QLQ-C30 and the EORTC QLQ-BR23

In the dossier, the pharmaceutical company presented separate analyses using constrained longitudinal data analysis (cLDA) for the neoadjuvant and adjuvant treatment phases - as outlined above for the endpoint of symptomatology - and presented the results of the change from baseline of the respective treatment phase as well as the mean differences between the study arms. In addition, the scores for each scale were reported descriptively for specific time points in the course of the study. The pharmaceutical company had not submitted evaluations of the entire course of the study. However, a separate evaluation of the neoadjuvant and adjuvant treatment phases is - as described above - inappropriate.

Within the framework of the written statement procedure, the pharmaceutical company submitted evaluations by means of constrained Longitudinal Data Analysis (cLDA) over both treatment phases of the KEYNOTE 522 study.

As outlined above for the endpoints of symptomatology and health status, the analyses presented include the comparison from the start of the neoadjuvant treatment phase to week 24 of the adjuvant treatment phase. Therefore, from the data presented, statements can only be made about a treatment duration of approx. 1 year and not about the entire course of the study up to 2 years after randomisation.

In IQWiG's view, the data presented here are not interpretable for the same reasons as outlined above for the endpoints of symptomatology and health status.

Thus, no assessable data are available overall for the endpoint of quality of life.

Side effects

Adverse events (AEs)

In the KEYNOTE 522 study, an adverse event occurred in 99.2% of premenopausal patients in the intervention arm and 100% thereof in the comparator arm. The results are only presented additionally.

Serious adverse events (SAEs) and discontinuation due to AEs

For the endpoints of SAE, severe AE and discontinuation due to AEs, there was a statistically significant disadvantage of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) compared with the appropriate comparator therapy.

Severe adverse events (CTCAE grade ≥ 3)

For the endpoint of severe adverse events (AEs), no statistically significant difference was detected between the treatment groups.

Specific adverse events

For specific AEs immune-mediated SAEs, immune-mediated severe AEs, blood and lymphatic system disorders (SAEs), injury, poisoning and procedural complications (SAEs), endocrine disorders (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary disorders (severe AEs) as well as skin and subcutaneous tissue disorders (severe AEs), there is a statistically significant difference in each case to the disadvantage of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) compared with the appropriate comparator therapy.

In summary, due to the disadvantages in the endpoints of SAE and discontinuation due to AEs, an overall disadvantage in side effects was found for the treatment with pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant). With regard to specific adverse events, there are detailed disadvantages of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant).

Overall assessment

For the benefit assessment of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) for the treatment of locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence, results from the ongoing, double-blind, randomised, controlled study KEYNOTE 522 on the endpoint categories of mortality, morbidity, health-related quality of life and side effects are available.

In the endpoint category of mortality, for the endpoint of overall survival, there is no statistically significant difference between the study arms.

In the morbidity category, the analysis of recurrences, operationalised via the recurrence rate and event-free survival shows a statistically significant difference to the advantage of pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant).

No assessable data are available for the endpoints of symptomatology and health status.

Likewise, no assessable data are available for the quality of life category.

With regard to side effects, there are statistically significant disadvantages for the endpoints of serious adverse events (SAE) and discontinuation due to AEs for treatment with pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) and in detail also for the specific AEs.

In the overall analysis, the relevant advantage with regard to the avoidance of recurrences is offset by the disadvantages in terms of side effects. The disadvantages in terms of side effects are weighted against the background that the avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

In a weighing decision, the G-BA comes to the conclusion that the advantage for the endpoint of recurrences outweighs the disadvantages of side effects and that overall, there is a moderate and not only minor improvement in the therapy-relevant benefit. Therefore, a minor additional benefit was identified for pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab in combination with doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) compared to treatment with paclitaxel and carboplatin, followed by doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and monitoring wait-and-see approach (adjuvant) in the treatment of locally advanced, triple-negative breast cancer or early-stage triple-negative breast cancer with a high risk of recurrence.

Reliability of data (probability of additional benefit)

The underlying KEYNOTE 522 study is a double-blind, randomised, controlled trial.

The risk of bias across endpoints for the KEYNOTE 522 study is rated as low at study level.

Overall, the reliability of the results is nevertheless reduced across the board. This results from the fact that platinum-based chemotherapy is not an appropriate treatment for all patients due to the higher haematological toxicity. In addition, medicinal products with a platinum active ingredient, such as the active ingredient carboplatin used in combination with pembrolizumab in the KEYNOTE 522 study, are neither approved for adjuvant nor neoadjuvant therapy of breast cancer. According to the present therapeutic indication of pembrolizumab, other chemotherapy combinations - including platinum-free chemotherapy combinations - would also be possible.

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

a) Pembrolizumab in combination with chemotherapy other than paclitaxel and carboplatin followed by pembrolizumab in combination with chemotherapy other than doxorubicin or epirubicin and cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

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

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of pembrolizumab finds its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The present results on overall survival are based on the 4th data cut-off from 23.03.2021 of the KEYNOTE 522 study. Further interim analyses were planned about 5 years after randomisation of the first patient, as well as one year after the 5th data cut-off and one year after the 6th data cut-off. The final analysis for event-free survival is planned after 327 events,

unless the study is discontinued prematurely. The interim analyses as well as the final analysis were originally planned as evaluations of the endpoint of event-free survival. However, it is clear from the documentation of the pharmaceutical company that after the 4th data cut-off no further confirmatory testing for event-free survival, but confirmatory testing for overall survival is carried out, since with the 4th data cut-off the null hypothesis for event-free survival could be rejected.

Since further clinical data from the KEYNOTE 522 study are expected, which may be relevant for the benefit assessment of the medicinal product, it is justified to limit the period of validity of the present resolution.

Conditions of the limitation:

For the new benefit assessment after the deadline, the results on all patient-relevant endpoints from the KEYNOTE 522 study must be submitted in the dossier by the 7th data cut-off planned for 23 March 2024.

A limitation for the resolution until 1 October 2024 is considered to be appropriate.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of the medicinal product pembrolizumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of pembrolizumab in comparison with the appropriate comparator therapy (Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5, Section 8, No. 5 VerfO). If the assessment is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product pembrolizumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 to 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab + chemotherapy for neoadjuvant treatment and then after surgery as monotherapy for adjuvant treatment. The therapeutic indication assessed here is as follows:

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence.

Since the assessment is based solely on data from the KEYNOTE 522 study for pembrolizumab + paclitaxel + carboplatin, followed by pembrolizumab + doxorubicin or epirubicin + cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant), but not in combination with

another chemotherapy, separate statements on the additional benefit are made in this regard:

a) Pembrolizumab + paclitaxel + carboplatin, followed by pembrolizumab + doxorubicin/epirubicin + cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

b) Pembrolizumab + chemotherapy other than paclitaxel and carboplatin, followed by pembrolizumab + chemotherapy other than doxorubicin or epirubicin + cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant)

Assessment of the additional benefit for a)

For the endpoint of overall survival, no statistically significant difference is detected between the treatment groups.

The analysis of recurrences, operationalised via the recurrence rate and event-free survival, shows a statistically significant advantage for patients who were treated in the intervention arm.

No assessable data are available for the endpoints of symptomatology and health status.

Likewise, no assessable data are available for the quality of life category.

The relevant advantage in recurrences is offset by disadvantages of the intervention treatment in the side effects category, particularly in the endpoints of serious adverse events (SAE) and discontinuation due to AEs, which, however, do not fundamentally call into question the advantages in recurrences against the background of the essential importance of avoiding recurrences in the curative treatment setting.

Overall, the reliability of data is rated as hint. This results from the fact that platinum-based chemotherapy is not an appropriate treatment for all patients. In addition, medicinal products with a platinum active ingredient are not approved for the present treatment setting. According to the present therapeutic indication, other chemotherapy combinations would also be possible.

Therefore, the overall conclusion is that there is a hint for a minor additional benefit of pembrolizumab + paclitaxel + carboplatin, followed by pembrolizumab + doxorubicin/epirubicin + cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant).

The resolution is limited for this patient group until 01.10.2024, as further clinical data from the KEYNOTE 522 study are expected.

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.

The resolution for this group of patients is limited until 01.10.2024.

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

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

The resolution is based on the information from the dossier of the pharmaceutical company. However, the number of patients estimated by the pharmaceutical company is subject to uncertainties. Among other things, there are uncertainties due to the unclear number of unconsidered patients with new local recurrence and in the percentage values for locally advanced, or early-stage breast cancer at high risk of recurrence as well as in the percentage value of triple-negative breast cancer, which may refer to patients outside the therapeutic indication.

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: 1 July 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 who are experienced in the treatment of patients with breast cancer, as well as specialists in obstetrics and gynaecology, and other specialists participating in the Oncology Agreement.

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 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 therapy regimen presented corresponds to the regimen used in the approval study of the therapeutic indication under consideration. The corresponding dosage information was taken from module 3 of the benefit assessment dossier and from the product information, section 5.1, of the pharmaceutical company.

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)[2]. This results in a body surface area of 1.76 m² (calculated according to Du Bois 1916).

For the calculation of the AUC dosage data of carboplatin, the mean age of women in Germany of 44.5 years[3], a gender factor of women of 0.85[4] and a mean serum creatinine concentration of 0.75 mg/dl[5] were also used.

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).[6]

Thus, a variety of different chemotherapies and treatment regimens may be considered with respect to the chemotherapy component. Therefore, the treatment costs for "pembrolizumab in combination with chemotherapy other than that mentioned in the approval study" are reported as not determinable.

Treatment period:

Neoadjuvant therapy:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Patient population a)				
Pembrolizumab	1 x every 21 days	8.0	1	8.0
	or			
	1 x every 42 days	4.0	1	4.0
in combination with				
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide				
Paclitaxel	on day 1, 8 and 15 of a 21-day cycle	4.0	3.0	12.0
Carboplatin	on day 1 of a	4.0	1.0	4.0

[2] Federal Health Reporting. Average body measurements of the population (2017), www.gbe-bund.de
[3] Federal Statistical Office (DESTATIS). Body measurements by age group and sex. 2022, https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Gesundheit/Gesundheitszustand-Relevantes-Verhalten/Tabellen/liste-koerpermasse.html
[4] Carboplatin AUC Calculator, https://www.thecalculator.co/health/Carboplatin-AUC-Calculator-631.html
[5] DocCheck Medical Services GmbH. DocCheck Flexikon - Serum creatinine. 2022, https://flexikon.doccheck.com/de/Serumkreatinin#
[6] Keytruda - European Public Assessement Report (EPAR) - https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0110-epar-assessment-report-variation_en.pdf

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	21-day cycle or on day 1, 8 and 15 of a 21-day cycle		 or 3.0	 or 12.0
Doxorubicin	on day 1 of a 21-day cycle	4.0	1.0	4.0
Cyclophosphamide	on day 1 of a 21-day cycle	4.0	1.0	4.0
or				
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide				
Paclitaxel	on day 1, 8 and 15 of a 21-day cycle	4.0	3.0	12.0
Carboplatin	on day 1 of a 21-day cycle or on day 1, 8 and 15 of a 21-day cycle	4.0	1.0 or 3.0	4.0 or 12.0
Epirubicin	on day 1 of a 21-day cycle	4.0	1.0	4.0
Cyclophosphamide	on day 1 of a 21-day cycle	4.0	1.0	4.0
Patient population b)				
Chemotherapy other than the one mentioned in the approval study				
Other chemotherapy	Not determinable			
Appropriate comparator therapy				
Patient populations a) + b)				
Therapy according to doctor's instructions[7]	No data available			

[7] For the present benefit assessment, a sequential or combined chemotherapy regimen containing a taxane and an anthracycline is a suitable comparator in the context of a therapy according to doctor's instructions in the neoadjuvant phase. However, taxanes are not approved in the present therapeutic indication and therefore, the costs are not represented.

Adjuvant therapy:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Patient populations a) + b)				
1st treatment year				
Pembrolizumab	1 x every 21 days	9.0	1	9.0
	or			
	1 x every 42 days	5.0	1	5.0
Subsequent years				
Pembrolizumab	1 x every 21 days	17.4	1	17.4
	or			
	1 x every 42 days	8.7	1	8.7
Appropriate comparator therapy				
Patient populations a) + b)				
Monitoring wait-and-see approach	Different from patient to patient			

Consumption:

Neoadjuvant therapy:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient population a)					
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					
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide					
Paclitaxel	80 mg/m² = 140.8 mg	140.8 mg	1 x 150 mg	12.0	12.0 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
Carboplatin	AUC 5 = 641.4 mg or AUC 1.5 = 192.4 mg	641.4 mg or 192.4 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg + 1 x 50 mg	4.0 or 12.0	4.0 x 600 mg + 4.0 x 50 mg or 12.0 x 150 mg + 12.0 x 50 mg
Doxorubicin	60 mg/m² = 105.6 mg	105.6 mg	2 x 50 mg + 1 x 10 mg	4.0	8.0 x 50 mg + 4.0 x 10 mg
Cyclophosphamide	600 mg/m² = 1,056 mg	1056 mg	1 x 1000 mg + 1 x 200 mg	4	4.0 x 1000 mg + 4.0 x 200 mg
or					
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide					
Paclitaxel	80 mg/m² = 140.8 mg	140.8 mg	1 x 150 mg	12.0	12.0 x 150 mg
Carboplatin	AUC 5 = 641.4 mg or AUC 1.5 = 192.4 mg	641.4 mg or 192.4 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg + 1 x 50 mg	4.0 or 12.0	4.0 x 600 mg + 4.0 x 50 mg or 12.0 x 150 mg + 12.0 x 50 mg
Epirubicin	90 mg/m² = 158.4 mg	158.4 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	4.0	4.0 x 100 mg + 4.0 x 50 mg + 4.0 x 10 mg
Cyclophosphamide	600 mg/m² = 1,056 mg	1056 mg	1 x 1000 mg + 1 x 200 mg	4	4.0 x 1000 mg + 4.0 x 200 mg
Patient population b)					
Chemotherapy other than the one mentioned in the approval study					
Other chemotherapy	Not determinable				
Appropriate comparator therapy					
Patient populations a) + b)					
Therapy according to doctor's instructions[7]	No data available				

Adjuvant therapy:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient populations a) + b)					
1st treatment year					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	9.0	18 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	5.0	20 x 100 mg
Subsequent years					
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
Appropriate comparator therapy					
Patient populations a) + b)					
Monitoring wait-and-see approach	Different from patient to patient				

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 100 mg	1 CIS	€ 3,035.99	€ 1.77	€ 170.10	€ 2,864.12
Carboplatin 50 mg	1 CIS	€ 34.63	€ 1.77	€ 1.11	€ 31.75
Carboplatin 150 mg	1 CIS	€ 83.03	€ 1.77	€ 3.40	€ 77.86
Carboplatin 600 mg	1 CIS	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Cyclophosphamide 200 mg	10 PSI	€ 62.76	€ 1.77	€ 2.85	€ 58.14
Cyclophosphamide 1000 mg	1 PSI	€ 30.63	€ 1.77	€ 1.07	€ 27.79
Doxorubicin 10 mg[8]	1 CIS	€ 40.28	€ 1.77	€ 2.29	€ 36.22
Doxorubicin 50 mg[8]	1 CIS	€ 151.23	€ 1.77	€ 11.07	€ 138.39

[8] 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
Epirubicin 10 mg	1 CIS	€ 39.47	€ 1.77	€ 1.34	€ 36.36
Epirubicin 50 mg	1 CIS	€ 155.41	€ 1.77	€ 6.84	€ 146.80
Epirubicin 100 mg	1 CIS	€ 300.81	€ 1.77	€ 13.74	€ 285.30
Paclitaxel 150 mg	1 CIS	€ 450.83	€ 1.77	€ 20.86	€ 428.20
Appropriate comparator therapy					
Not applicable					
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					

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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.

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	12.0	€ 56.20
Dimetindene IV 1 mg/10 kg	5 x 4 mg SFI	€ 23.67	€ 1.77	€ 5.58	€ 16.32	12.0	€ 78.34
Cimetidine IV 300 mg	10 AMP each 200 mg	€ 19.77	€ 1.77	€ 0.40	€ 17.60	12.0	€ 42.24
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 € 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 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.

2.5 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 Pembrolizumab

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 12 June 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

After the positive opinion was issued, the appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 8 June 2022.

On 16 June 2022, 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 23 June 2022 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 29 September 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 4 October 2022. The deadline for submitting written statements was 25 October 2022.

The oral hearing was held on 7 November 2022.

By letter dated 8 November 2022, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 25 November 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 6 December 2022, and the proposed resolution was approved.

At its session on 15 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 June 2018	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	8 June 2022	New determination of the appropriate comparator therapy
Working group Section 35a	1 November 2022	Information on written statements received; preparation of the oral hearing

Subcommittee Medicinal products	7 November 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 November 2022 29 November 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 December 2022	Concluding discussion of the draft resolution
Plenum	15 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 December 2022

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

Prof. Hecken