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 (reassessment after the deadline: breast cancer, triple-negative, high risk of recurrence, neoadjuvant and adjuvant therapy, monotherapy or combination with chemotherapy)

of 20 March 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The pharmaceutical company submitted a dossier for the early benefit assessment of the active ingredient pembrolizumab (Keytruda) to be assessed for the first time on 16 June 2022. For the resolution of 15 December 2022 made by the G-BA in this procedure, a limitation up to 1 October 2024 was pronounced.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO, the procedure for the benefit assessment of the medicinal product Keytruda recommences when the deadline has expired.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO on 22 August 2024.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of pembrolizumab compared to 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. 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 20.03.2025):

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 for pembrolizumab in combination with chemotherapy for neoadjuvant treatment followed by pembrolizumab as monotherapy for adjuvant treatment after surgery:

An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of:

- Cyclophosphamide

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

- Docetaxel
- Doxorubicin
- Epirubicin
- Paclitaxel
- Carboplatin

followed by monitoring wait-and-see approach after surgery

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

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

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

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

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

On 1. For the present therapeutic indication, the active ingredients doxorubicin, epirubicin, 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.

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

- Olaparib: resolution of 16 February 2023

Directive on Examination and Treatment Methods in Hospitals (Directive on Inpatient Treatment Methods) - 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 for off-label use:

- Gemcitabine in monotherapy for breast cancer in women

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. In the present procedure, no written opinion on the question of appropriate comparator therapy was received from the scientific-medical societies or the Drugs Commission of the German Medical Association (AkdÄ).

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 guideline[2], 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

[2] Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J Clin Oncol 2021;39(13):1485-1505.

considered both adjuvant and neoadjuvant. For neoadjuvant treatment of breast cancer, the same chemotherapy combinations as for adjuvant treatment are generally recommended according to the current guideline.

Accordingly, the current guideline recommends taxane and anthracycline-based chemotherapy for neoadjuvant treatment. 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, cyclophosphamide and docetaxel are approved for adjuvant therapy, but not for the neoadjuvant treatment setting, but are also recommended for neoadjuvant therapy.

Meta-analyses have also shown that the addition of carboplatin improves overall survival (OS) and disease-free survival (DFS).[3] The active ingredient carboplatin is not approved in the present therapeutic indication for either the adjuvant or the neoadjuvant treatment setting. The available evidence shows that carboplatin is a possible therapy option. At their session on 19 October 2023, the G-BA decided to commission the Expert Group on Off-Label Use in accordance with Section 35c, paragraph 1 SGB V (off-label expert group) to assess the state of scientific knowledge on platinum derivatives or platinum complexes (cisplatin/ carboplatin) for early-stage triple-negative breast cancer.

In accordance with the generally recognised state of medical knowledge, it should be noted that the off-label use of the above-mentioned therapy options cyclophosphamide, docetaxel, paclitaxel and carboplatin shall generally be preferred over the medicinal products previously approved for this therapeutic indication. It is therefore appropriate to determine the off-label use of the above-mentioned medicinal products as the appropriate comparator therapy according to Section 6, paragraph 2, sentence 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

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.

In the overall assessment, individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel and carboplatin followed by monitoring wait-and-see approach after surgery is determined as the appropriate comparator therapy in this therapeutic indication.

Editorial note: The term "individualised therapy" is used instead of previously used terms such as "patient-individual therapy" or "therapy according to doctor's instructions". This harmonises the terms used in the European assessment procedures (EU-HTA).

[3] Mason SRE, Willson ML, Egger SJ, Beith J, Dear RF, Goodwin A. Platinum-based chemotherapy for early triple-negative breast cancer. Cochrane Database of Systematic Reviews [online]. 2023(9):Cd014805. URL: http://dx.doi.org/10.1002/14651858.CD014805.pub2.

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 an indication of 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 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) for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence is not proven.

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).

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.

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).

On the implementation of the time limit requirements

According to the justification of the resolution of 15 December 2022, the reason for the limitation was that further clinical data from the KEYNOTE 522 study were expected, which may be relevant for the benefit assessment.

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.

The pharmaceutical company presented the required evaluations in the dossier, so that the time limit requirements are considered to have been implemented overall.

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.[4]

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.

[4] Keytruda - European Public Assessment Report (EPAR) - EMEA/H/C/003820/II/0110; https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0110-epar-assessment-report-variation_en.pdf

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.

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, there was a statistically significant difference to the advantage of the combination therapy with pembrolizumab. The extent of the prolongation achieved in overall survival is assessed as a relevant improvement.

Morbidity

Failure of the curative therapeutic approach (event 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, the endpoint is considered with the endpoint of event rate as well as with 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
- Distant recurrence
- Distant 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 event 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 the failure of the curative therapeutic approach 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 statements of clinical experts in the initial assessment 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 evaluations for the 7th data cut-off for the scales of the EORTC QLQ-C30 and the EORTC QLQ-BR23 as well as for the VAS of the EQ-5D. Both treatment phases of the KEYNOTE 522 study (neoadjuvant and adjuvant) were analysed using a cLDA model (constrained longitudinal data analysis) from the start of treatment to the long-term follow-up 12 months after randomisation.

The patient-reported endpoints were assessed according to the study protocol at the beginning of cycles 1, 5 and 8 of the neoadjuvant treatment phase and cycles 1, 5 and 9 of the adjuvant treatment phase, provided that there was no therapy discontinuation by then. In addition, assessments were planned 12 months and 24 months after randomisation as part of the long-term follow-up. This included patients upon therapy discontinuation or completion of adjuvant treatment. An exception was therapy discontinuation due to progression or recurrence, in which case there was no transfer to the long-term follow-up but the observation ended. The period immediately following therapy discontinuation is therefore not recorded in any of the assessments included in the evaluations.

In addition, the operationalisation results in variable time periods between the neoadjuvant and adjuvant treatment phases during which no patient-reported endpoints were assessed. The period between the neoadjuvant and adjuvant treatment phases is part of the study, so the questionnaires should continuously be collected further. Furthermore, no information is available regarding the period and whether it differs between the study arms.

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 avoidance of the failure of the curative therapeutic approach. 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.

<u>Quality of life</u>

EORTC QLQ-C30 and the EORTC QLQ-BR23

In the dossier, the pharmaceutical company presented evaluations for the 7th data cut-off for the scales of the EORTC QLQ-C30 and the EORTC QLQ-BR23.

As described above for the endpoint of symptomatology, both treatment phases of the KEYNOTE 522 study (neoadjuvant and adjuvant) were analysed using a cLDA model

(constrained longitudinal data analysis) from the start of treatment to the long-term follow-up 12 months after randomisation.

As already described for the endpoint of symptomatology, no assessable data are available 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 patients in the intervention arm and 100% thereof in the comparator arm. The results were only presented additionally.

Serious adverse events (SAEs) and discontinuation due to AEs

For the endpoints of SAEs and therapy discontinuation due to AEs, there was a statistically significant disadvantage for the combination therapy with pembrolizumab compared with the appropriate comparator therapy.

Severe adverse events (CTCAE grade ≥ 3)

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

Specific adverse events

For the specific AEs of immune-mediated SAE, immune-mediated severe AE, blood and lymphatic system disorders (SAE), injury, poisoning and procedural complications (SAE), endocrine disorders (severe AE), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AE), hepatobiliary disorders (severe AE) as well as skin and subcutaneous tissue disorders (severe AE), there was 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, there was a statistically significant difference in the overall survival endpoint to the advantage of combination therapy with pembrolizumab. The extent of the prolongation achieved in overall survival is assessed as a relevant improvement.

In the morbidity category, with regard to the failure of the curative therapeutic approach, operationalised via the event rate and event-free survival, there was 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 endpoint category of quality of life.

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 for the specific AEs.

In the overall analysis, the relevant improvement in the prolongation of overall survival and the relevant advantage in terms of avoidance of the failure of the curative therapeutic approach are offset by 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 their weighted decision, the G-BA comes to the conclusion that the advantages in overall survival and with regard to the avoidance of failure of the curative therapeutic approach outweigh the disadvantages in terms of side effects and that overall there is a relevant 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.

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

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)

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

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient pembrolizumab due to the expiry of the limitation of the resolution of 15 December 2022.

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.

Individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel and carboplatin followed by monitoring wait-and-see approach after surgery is determined as the appropriate comparator therapy.

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)

On patient group a)

In the endpoint of overall survival, there was a statistically significant difference to the advantage of the combination therapy with pembrolizumab.

The analysis of the failure of the curative therapeutic approach, operationalised via the event 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 as well as for the endpoint category of quality of life.

In the overall analysis, the relevant improvement in the prolongation of overall survival and the relevant advantage in terms of avoidance of the failure of the curative therapeutic approach are offset by 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.

As a result, a minor additional benefit of pembrolizumab + paclitaxel + carboplatin, followed by pembrolizumab + doxorubicin/ epirubicin + cyclophosphamide (neoadjuvant) and pembrolizumab (adjuvant) is identified.

The reliability of data of the additional benefit identified is classified in the "indication" category.

On patient group b)

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

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

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

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

The number of patients stated by the pharmaceutical company in the dossier is subject to uncertainties. Thus, there are also uncertainties due to the unclear number of unconsidered patients with, for example, newly occurring local recurrence and due to a possible underestimation of the percentage of patients with triple-negative breast cancer. Furthermore, more up-to-date data on the crude incidence rate of breast cancer is now available.

In the absence of more suitable data and against the background of the aspects presented, which indicate a potential underestimation, the resolution is based on a range formed from the lower limit of the underlying number of patients in the resolution of the initial assessment (resolution of 15 December 2022) and the upper limit of the information provided by the pharmaceutical company in the dossier for the present assessment for the SHI target population. It should be noted that the patient number is expected to be closer to the upper limit of the range.

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: 11 March 2025):

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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2025).

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 varies from patient to patient 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 the product information, section 5.1, of the pharmaceutical company.

For dosages depending on body weight (bw) or body surface area (BSA), the average body measurements of adult females from the official representative statistics “Microcensus 2021 – body measurements of the population” were applied (average body height: 1.66 m; average body weight: 69.2 kg)[5]. This results in a body surface area of 1.77 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 46 years[6], a gender factor of women of 0.85 and a mean serum creatinine concentration of 0.75 mg/dl were also used[7]. The dosage was determined using the Calvert equation, whereby the glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault formula.

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).[8]

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:

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

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

[5] Federal Health Reporting. Average body measurements of the population (2021, women, 15 years and older), https://www.gbe-bund.de/
[6] Federal Institute for Population Research, Average age of the population in Germany (1871-2021) https://www.bib.bund.de/DE/Fakten/Fakt/B19-Durchschnittsalter-Bevoelkerung-ab-1871.html
[7] DocCheck Flexikon – Serum creatinine, URL: https://flexikon.doccheck.com/de/Serumkreatinin [last access: 05.02.2025]
[8] 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
Medicinal product to be assessed				
Neoadjuvant therapy:				
Pembrolizumab	1 x every 21 days or 1 x every 42 days	8.0 or 4.0	1	8.0 or 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	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 or 3	4.0 or 12.0
Doxorubicin	on day 1 of a 21-day cycle	4.0	1	4.0
Cyclophosphamide	on day 1 of a 21-day cycle	4.0	1	4.0
In combination with paclitaxel and carboplatin followed by epirubicin and cyclophosphamide				
Paclitaxel	on day 1, 8 and 15 of a 21-day cycle	4.0	3	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 or 3	4.0 or 12.0
Epirubicin	on day 1 of a 21-day cycle	4.0	1	4.0
Cyclophosphamide	on day 1 of a 21-day cycle	4.0	1	4.0
Adjuvant therapy:				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Pembrolizumab	1 x every 21 days or 1 x every 42 days	9.0 or 5.0	1	9.0 or 5.0
Appropriate comparator therapy				
An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of: Cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel, carboplatin followed by monitoring wait-and-see approach				
Neoadjuvant therapy:				
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide				
Paclitaxel	on day 1, 8 and 15 of a 21-day cycle	4.0	3	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 or 3	4.0 or 12.0
Doxorubicin	on day 1 of a 21-day cycle	4.0	1	4.0
Cyclophosphamide	on day 1 of a 21-day cycle	4.0	1	1.0
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide				
Paclitaxel	on day 1, 8 and 15 of a 21-day cycle	4.0	3	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 or 3	4.0 or 12.0
Epirubicin	on day 1 of a 21-day cycle	4.0	1	4.0
Cyclophosphamide	on day 1 of a	4.0	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	21-day cycle			
Docetaxel in combination with doxorubicin and cyclophosphamide[9]				
Doxorubicin	1 x every 21 days	6.0	3	18.0
Cyclophosphamide	1 x every 21 days	6.0	3	18.0
Docetaxel	1 x every 21 days	6.0	3	18.0
Adjuvant therapy:				
Monitoring wait-and-see approach	Different from patient to patient			

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)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Neoadjuvant therapy:				
Pembrolizumab	1 x every 21 days or 1 x every 42 days	8.0 or 4.0	1	8.0 or 4.0
In combination with a chemotherapy other than the one mentioned in the approval study				
Other chemotherapy	Not determinable			
Adjuvant therapy:				
Pembrolizumab	1 x every 21 days	9.0 or	1	9.0 or

[9] See the product information for docetaxel

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	or 1 x every 42 days	5.0		5.0
Appropriate comparator therapy				
An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of: Cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel, carboplatin followed by monitoring wait-and-see approach				
Neoadjuvant therapy:				
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide				
Paclitaxel	on day 1, 8 and 15 of a 21-day cycle	4.0	3	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 or 3	4.0 or 12.0
Doxorubicin	on day 1 of a 21-day cycle	4.0	1	4.0
Cyclophosphamide	on day 1 of a 21-day cycle	4.0	1	4.0
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide				
Paclitaxel	on day 1, 8 and 15 of a 21-day cycle	4.0	3	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 or 3	4.0 or 12.0
Epirubicin	on day 1 of a 21-day cycle	4.0	1	4.0
Cyclophosphamide	on day 1 of a 21-day cycle	4.0	1	4.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Docetaxel in combination with doxorubicin and cyclophosphamide[8]				
Doxorubicin	1 x every 21 days	6.0	3	18.0
Cyclophosphamide	1 x every 21 days	6.0	3	18.0
Docetaxel	1 x every 21 days	6.0	3	18.0
Adjuvant therapy:				
Monitoring wait-and-see approach	Different from patient to patient			

Consumption:

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

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

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					
Neoadjuvant therapy:					
Pembrolizumab	200 mg or 400 mg	200 mg or 400 mg	2 x 100 mg or 4 x 100 mg	8.0 or 4.0	16 x 100 mg
In combination with paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide					
Paclitaxel	80 mg/m²= 141.6 mg	141.6 mg	1 x 150 mg	12.0	12 x 150 mg
Carboplatin	AUC 5 = 636.9 mg or	636.9 mg or 191.1 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg+	4.0 or 12.0	4 x 600 mg + 4 x 50 mg or

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	AUC 1.5 = 191.1 mg		1 x 50 mg		12 x 150 mg + 12 x 50 mg
Doxorubicin	60 mg/m² = 106.2 mg	106.2 mg	1 x 100 mg + 1 x 10 mg	4.0	4 x 100 mg + 4 x 10 mg
Cyclophosphamide	600 mg/m² = 1,062 mg	1,062 mg	1 x 1,000 mg + 1 x 200 mg	4.0	4 x 1,000 mg + 4 x 200 mg
In combination with paclitaxel and carboplatin followed by epirubicin and cyclophosphamide					
Paclitaxel	80 mg/m²= 141.6 mg	141.6 mg	1 x 150 mg	12.0	12 x 150 mg
Carboplatin	AUC 5 = 636.9 mg or AUC 1.5 = 191.1 mg	636.9 mg or 191.1 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg+ 1 x 50 mg	4.0 or 12.0	4 x 600 mg + 4 x 50 mg or 12 x 150 mg + 12 x 50 mg
Epirubicin	90 mg/m² = 159.3 mg	159.3 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	4.0	4 x 100 mg + 4 x 50 mg + 4 x 10 mg
Cyclophosphamide	600 mg/m² = 1,062 mg	1,062 mg	1 x 1,000 mg + 1 x 200 mg	4.0	4 x 1,000 mg + 4 x 200 mg
Adjuvant therapy:					
Pembrolizumab	200 mg or 400 mg	200 mg or 400 mg	2 x 100 mg or 4 x 100 mg	9.0 or 5.0	18 x 100 mg or 20 x 100 mg
Appropriate comparator therapy					
An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of: Cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel, carboplatin followed by monitoring wait-and-see approach					
Neoadjuvant therapy:					
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide					
Paclitaxel	80 mg/m²= 141.6 mg	141.6 mg	1 x 150 mg	12.0	12 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 = 636.9 mg or AUC 1.5 = 191.1 mg	636.9 mg or 191.1 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg+ 1 x 50 mg	4.0 or 12.0	4 x 600 mg + 4 x 50 mg or 12 x 150 mg + 12 x 50 mg
Doxorubicin	60 mg/m² = 106.2 mg	106.2 mg	1 x 100 mg + 1 x 10 mg	4.0	4 x 100 mg + 4 x 10 mg
Cyclophosphamide	600 mg/m² = 1,062 mg	1,062 mg	1 x 1,000 mg + 1 x 200 mg	4.0	4 x 1,000 mg + 4 x 200 mg
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide					
Paclitaxel	80 mg/m²= 141.6 mg	141.6 mg	1 x 150 mg	12.0	12 x 150 mg
Carboplatin	AUC 5 = 636.9 mg or AUC 1.5 = 191.1 mg	636.9 mg or 191.1 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg+ 1 x 50 mg	4.0 or 12.0	4 x 600 mg + 4 x 50 mg or 12 x 150 mg + 12 x 50 mg
Epirubicin	90 mg/m² = 159.3 mg	159.3 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	4.0	4 x 100 mg + 4 x 50 mg + 4 x 10 mg
Cyclophosphamide	600 mg/m² = 1,062 mg	1,062 mg	1 x 1,069 mg	12.0	12 x 1,069 mg
Docetaxel in combination with doxorubicin and cyclophosphamide[8]					
Doxorubicin	50 mg/m² = 88.5 mg	88.5 mg	1 x 50 mg + 4 x 10 mg	18.0	18 x 50 mg + 72 x 10 mg
Cyclophosphamide	500 mg/m² = 885 mg	885 mg	1 x 1,000 mg	18.0	18 x 1,000 mg
Docetaxel	75 mg/m²= 132.75 mg	132.75 mg	1 x 140 mg	18.0	18 x 140 mg
Adjuvant therapy:					
Monitoring wait-and-see approach	Different from patient to patient				

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)

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					
Neoadjuvant therapy:					
Pembrolizumab	200 mg or 400 mg	200 mg or 400 mg	2 x 100 mg or 4 x 100 mg	8.0 or 4.0	16 x 100 mg
In combination with a chemotherapy other than the one mentioned in the approval study					
Other chemotherapy	Not determinable				
Adjuvant therapy:					
Pembrolizumab	200 mg or 400 mg	200 mg or 400 mg	2 x 100 mg or 4 x 100 mg	9.0 or 5.0	18 x 100 mg or 20 x 100 mg
Appropriate comparator therapy					
An individualised taxane and anthracycline-based neoadjuvant chemotherapy with selection of: Cyclophosphamide, docetaxel, doxorubicin, epirubicin, paclitaxel, carboplatin followed by monitoring wait-and-see approach					
Neoadjuvant therapy:					
paclitaxel and carboplatin followed by doxorubicin and cyclophosphamide					
Paclitaxel	80 mg/m²= 141.6 mg	141.6 mg	1 x 150 mg	12.0	12 x 150 mg
Carboplatin	AUC 5 = 636.9 mg or AUC 1.5 = 191.1 mg	636.9 mg or 191.1 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg+ 1 x 50 mg	4.0 or 12.0	4 x 600 mg + 4 x 50 mg or 12 x 150 mg + 12 x 50 mg
Doxorubicin	60 mg/m² = 106.2 mg	106.2 mg	1 x 100 mg + 1 x 10 mg	4.0	4 x 100 mg + 4 x 10 mg
Cyclophosphamide	600 mg/m² = 1,062 mg	1,062 mg	1 x 1,000 mg + 1 x 200 mg	4.0	4 x 1,000 mg + 4 x 200 mg
Paclitaxel and carboplatin followed by epirubicin and cyclophosphamide					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Paclitaxel	80 mg/m²= 141.6 mg	141.6 mg	1 x 150 mg	12.0	12 x 150 mg
Carboplatin	AUC 5 = 636.9 mg or AUC 1.5 = 191.1 mg	636.9 mg or 191.1 mg	1 x 600 mg + 1 x 50 mg or 1 x 150 mg+ 1 x 50 mg	4.0 or 12.0	4 x 600 mg + 4 x 50 mg or 12 x 150 mg + 12 x 50 mg
Epirubicin	90 mg/m² = 159.3 mg	159.3 mg	1 x 100 mg + 1 x 50 mg + 1 x 10 mg	4.0	4 x 100 mg + 4 x 50 mg + 4 x 10 mg
Cyclophosphamide	600 mg/m² = 1,062 mg	1,062 mg	1 x 1,000 mg + 1 x 200 mg	4.0	4 x 1,000 mg + 4 x 200 mg
Docetaxel in combination with doxorubicin and cyclophosphamide[8]					
Doxorubicin	50 mg/m² = 88.5 mg	88.5 mg	1 x 50 mg + 4 x 10 mg	18.0	18 x 50 mg + 72 x 10 mg
Cyclophosphamide	500 mg/m² = 885 mg	885 mg	1 x 1,000 mg	18.0	18 x 1,000 mg
Docetaxel	75 mg/m²= 132.75 mg	132.75 mg	1 x 140 mg	18.0	18 x 140 mg
Adjuvant therapy:					
Monitoring wait-and-see approach	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Patient populations a) and b)

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pembrolizumab 100 mg	1 CIS	€ 2,743.07	€ 1.77	€ 153.37	€ 2,587.93
Carboplatin 600 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Carboplatin 150 mg	1 CIS	€ 83.06	€ 1.77	€ 3.40	€ 77.89
Carboplatin 50 mg	1 CIS	€ 34.66	€ 1.77	€ 1.11	€ 31.78
Cyclophosphamide 1,000 mg	6 PSI	€ 142.80	€ 1.77	€ 7.28	€ 133.75
Doxorubicin 100 mg[10]	1 CIS	€ 285.79	€ 1.77	€ 0.00	€ 284.02
Doxorubicin 10 mg	1 CIS	€ 40.32	€ 1.77	€ 2.29	€ 36.26
Epirubicin 100 mg	1 SFI	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Epirubicin 50 mg	1 SFI	€ 155.45	€ 1.77	€ 6.84	€ 146.84
Epirubicin 10 mg	1 CIS	€ 39.51	€ 1.77	€ 1.34	€ 36.40
Paclitaxel 150 mg	1 CIS	€ 428.97	€ 1.77	€ 19.82	€ 407.38
Appropriate comparator therapy					
Carboplatin 600 mg	1 CIS	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Carboplatin 150 mg	1 CIS	€ 83.06	€ 1.77	€ 3.40	€ 77.89
Carboplatin 50 mg	1 CIS	€ 34.66	€ 1.77	€ 1.11	€ 31.78
Cyclophosphamide 1,000 mg	6 PSI	€ 142.80	€ 1.77	€ 7.28	€ 133.75
Docetaxel 140 mg	1 CIS	€ 719.33	€ 1.77	€ 33.60	€ 683.96
Doxorubicin 100 mg[10]	1 CIS	€ 285.79	€ 1.77	€ 0.00	€ 284.02
Doxorubicin 50 mg[10]	1 CIS	€ 151.26	€ 1.77	€ 11.07	€ 138.42
Doxorubicin 10 mg[10]	1 CIS	€ 40.32	€ 1.77	€ 2.29	€ 36.26
Epirubicin 100 mg	1 SFI	€ 300.84	€ 1.77	€ 13.74	€ 285.33
Epirubicin 50 mg	1 SFI	€ 155.45	€ 1.77	€ 6.84	€ 146.84
Epirubicin 10 mg	1 CIS	€ 39.51	€ 1.77	€ 1.34	€ 36.40
Paclitaxel 150 mg	1 CIS	€ 428.97	€ 1.77	€ 19.82	€ 407.38
Abbreviations: CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection;					

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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

[10] Fixed reimbursement rate

expenditure in the course of the treatment are not shown.

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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 1 October 2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic agents a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs 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 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

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

Basic principles of the assessed medicinal product

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

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

A designation is also not considered if the G-BA has decided on an exemption as a reserve

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

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

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

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

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

Concomitant active ingredient

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

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

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

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

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

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

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

Designation

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

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

Exception to the designation

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

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

Legal effects of the designation

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

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

Justification for the findings on designation in the present resolution:

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

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

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

3. Bureaucratic costs calculation

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

4. Process sequence

At their session on 9 July 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 22 August 2024, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

By letter dated 30 September 2024 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products

with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 20 December 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2025. The deadline for submitting written statements was 23 January 2025.

The oral hearing was held on 10 February 2025.

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 11 March 2025, and the proposed draft resolution was approved.

At its session on 20 March 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	9 July 2024	Determination of the appropriate comparator therapy
Working group Section 35a	4 February 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	10 February 2025	Conduct of the oral hearing
Working group Section 35a	18 February 2025 4 March 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 March 2025	Concluding discussion of the draft resolution
Plenum	20 March 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 March 2025

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

Prof. Hecken