Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Pembrolizumab (new therapeutic indication: melanoma, adjuvant therapy)

of 19 September 2019

Contents

1. Legal basis

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

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

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

On 12 December 2018, pembrolizumab received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 number a, letter a to Regulation (EC) number 1234/2008 of the Commission from 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 December 2008, p. 7).

On 24 July 2018, the pharmaceutical company filed an application to consolidate the evaluation procedures for pembrolizumab according to Section 35a, paragraph 5b SGB V. At its session on 20 September 2018, the G-BA approved the application for consolidation in accordance with Section 35a, paragraph 5b SGB V.

On 28 March 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new

therapeutic indication “KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.”

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 July 2019 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. 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 comments received and the oral hearing, the G-BA has arrived at 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 product information

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection (see Section 5.1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection

Monitoring wait-and-see approach

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 according to 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.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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. Nivolumab and interferon-alpha-2b are authorised for use in this therapeutic indication. Furthermore, the combination therapy dabrafenib + trametinib is explicitly authorised for the adjuvant treatment of BRAF-V600 mutation-positive melanoma.

On 2. In principle, adjuvant radiotherapy can be considered in the present therapeutic indication.

On 3. The following resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V are available.

- Nivolumab: Resolution of 21 February 2019
- Dabrafenib: Resolution of 22 March 2019
- Trametinib: Resolution of 22 March 2019

On 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies.

Interferon alfa-2b is authorised for the treatment of patients who are tumour-free after surgery but who are at high risk of relapse. In connection with interferon therapy, the guidelines point out the possible side effects and the associated sometimes considerable impairment of quality of life. In view of the toxicity potential of the active ingredient and the heterogeneous study results for prolonging overall survival, interferon therapy for Stage IIIA-C patients is not recommended in the guidelines or should be offered as a treatment option after careful consideration of the expected advantages and disadvantages of the therapy. Regular use cannot be deduced from this, which is why interferon alfa-2b cannot be considered as an appropriate comparator therapy.

Furthermore, nivolumab has been available since July 2018 and the combination therapy dabrafenib + trametinib has been available since August 2018 for the sub-population of patients with BRAF-V600 mutations covered by the therapeutic indication under evaluation.

By resolution of 21 February 2019, the G-BA identified a hint for a non-quantifiable additional benefit for nivolumab. In this context, there were very clear advantages with regard to the prevention of relapses and relevant disadvantages because of side effects. However, partly because of a very short observation period and the fact that the assessment was based on an indirect comparison, the data were subject to significant uncertainties. The resolution is limited until 1 April 2021.

For the combination dabrafenib + trametinib, the G-BA determined in its resolution of 22 March 2019 that there was an indication of a considerable additional benefit. There were very clear advantages with regard to relapses and clear advantages in overall survival with simultaneously relevant disadvantages with regard to side effects. For the overall survival endpoint, the median survival time was not yet reached in both arms. The resolution is limited until 1 April 2024.

The therapeutic significance of nivolumab and the combination dabrafenib + trametinib cannot yet be conclusively assessed.

Therefore, nivolumab and the combination therapy dabrafenib + trametinib have not been identified as appropriate comparator therapy at this time.

In principle, adjuvant radiotherapy can be considered as non-medicinal treatment for Stage III patients. This serves to improve regional tumour control. Adjuvant radiotherapy is used on a patient-individual basis depending on the risk of relapse and after weighing possible therapy-related side effects. There are no data that show a positive influence of adjuvant radiotherapy on overall survival. Regular use cannot be deduced, which is why adjuvant radiotherapy cannot be considered as an appropriate comparator therapy:

Therefore, in the overall view, a “monitoring wait-and-see approach” is defined as an appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

For pembrolizumab as monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection, there is an indication of a non-quantifiable additional benefit.

Justification:

The benefit assessment is based on the results of the randomised, double-blind, placebo-controlled KEYNOTE-054 study.

Included were patients with fully resected, histologically confirmed, cutaneous melanoma in Tumour stage III according to American Joint Committee on Cancer Version 7 (AJCC 7). However, patients with in transit or satellite metastases as well as Stage IIIA patients (according to AJCC 7) with lymph node metastases ≤ 1 mm were not included. Furthermore, patients with ECOG status > 1 were not included.

A total of 1019 patients were randomized 1:1 to the pembrolizumab arm (N = 514) or the placebo arm (N = 505). Stratification was performed by disease stage (IIIA, IIIB, IIIC [1–3 positive lymph nodes], IIIC [≥ 4 positive lymph nodes] according to AJCC 7) and geographic region (North America, Europe, Australia, and other). The patients were predominantly male and 54 years old on average. The ongoing study began in July 2015 and is conducted multicentrally in 134 centres in Europe, North America, Asia, and Australia.

Patients were treated over one year or 18 doses (every three weeks) or until relapse, unacceptable toxicity, onset of a new malignant disease, or therapy discontinuation at the physician’s or patient’s discretion.

Based on the KEYNOTE-054 study regime, the placebo comparison is regarded as a sufficient approximation to the appropriate comparator therapy, a monitoring wait-and-see approach.

The KEYNOTE-054 study consists of two parts. Part 1 covers initiative adjuvant therapy and subsequent observation time. After a relapse, patients may, under certain conditions, move to Part 2 and receive follow-up therapy with pembrolizumab. Patients who received pembrolizumab during Part 1 of the study can only receive follow-up therapy with pembrolizumab if the duration of the prior therapy with pembrolizumab lasted one year and the relapse occurred at the earliest six months after the end of the therapy. Part 2 of the study also included the subsequent observation period. Only patients who had transferred to Part 2 of the study continued to be systematically examined for disease progression or a second relapse.

For all endpoints, the pharmaceutical company presents only data for Part 1 of the study. These affects the 1st data cut-off of 2 October 2017 and the 2nd data cut-off of 2 May 2018 for the relapse-free survival (RFS) endpoint. The 1st data cut-off represents an interim analysis for the endpoint relapse-free survival after approx. 330 events introduced by a subsequent protocol change (dated 2 October 2017). The 2nd data cut-off was requested by the EMA for the endpoint relapse-free survival. In the benefit assessment, the 1st data cut-off is used for the endpoints of the adverse reactions category and the 2nd data cut-off is used for the endpoints of the relapse category because of the longer observation period. The high risk period for the occurrence of a relapse in the present therapeutic indication is three years after primary diagnosis. A median observation period of 21.6 months is available for the 2nd data cut-off. This means that the high-risk period for the occurrence of a relapse is not yet completely mapped at this time.

Because Stage IIIA patients with lymph node metastases ≤ 1 mm and patients with in-transit and satellite metastases were not included in the study, there are discrepancies between the study population and the target population covered by the therapeutic indication.

Extent and probability of the additional benefit

Mortality

Overall survival

In accordance with the study protocol, no evaluation of the overall survival endpoint was planned for the KEYNOTE-054 study at the time of the 1st and 2nd data cut-off. At the time of the 1st data cut-off, 25 patients in the pembrolizumab arm and 35 patients in the placebo arm had died.

Morbidity

Relapses/relapse-free survival

Patients in this therapeutic indication are treated with a curative therapy approach as part of the adjuvant treatment of melanoma after complete resection. Nevertheless, tumour cells can remain and cause a relapse in the further course. A relapse means that the attempt to cure the disease with the curative therapy approach was not successful. The occurrence of a relapse is patient-relevant.

The endpoints relapses and relapse-free survival include the following individual components:

- Local/regional relapse
- Remote metastases
- Local/regional relapse and remote metastases
- Death (of any cause)

The endpoint relapses describes the proportion of patients with a relapse event or death at the corresponding data cut-off (event rate). In the relapse-free survival endpoint, the time to the event (relapse or death) is also considered (event time analysis).

Relapses

For the relapses endpoint, a statistically significant advantage of pembrolizumab compared to a monitoring wait-and-see approach was observed at the time of the 2nd data cut off (Relative Risk (RR): 0.63; [95% confidence interval (CI): 0.54; 0.74]; p value < 0.001). 30.7% of the patients in the pembrolizumab arm and 48.7% in the placebo arm suffered a relapse up to the time of the 2nd data cut-off.

Relapse-free survival

With regard to the endpoint of relapse-free survival, there is a statistically significant advantage under therapy with pembrolizumab (hazard ratio (HR): 0.56; [95% CI: 0.44; 0.72]; $p < 0.001$). In the pembrolizumab arm, the median time to the event was not yet reached; in the comparator arm, it was 21.7 months.

Overall, in terms of the endpoints relapses and relapse-free survival, pembrolizumab shows a clear, clinically relevant advantage over a monitoring wait-and-see approach.

However, because the observation period (21.6 months median) for the 2nd data cut-off is relatively short and not long enough to adequately reflect the high risk period for the occurrence of a relapse of 3 years after primary diagnosis, the extent of this benefit cannot be clearly quantified based on the data available.

Symptomology EORTC QLQ-C30

In the KEYNOTE-054 study, the disease symptoms are assessed using the symptom scales of the cancer-specific questionnaire EORTC QLQ-C30. Exhaustion, nausea and vomiting, pain, dyspnoea, insomnia, loss of appetite, constipation and diarrhoea are recorded. The pharmaceutical company presented evaluations up to the first confirmed deterioration.

Only evaluations for Part 1 of the study were shown, although a survey should be conducted for 4 years regardless of a transition to Part 2 of the study. For patients who showed a deterioration by ≥ 10 points at the last survey time of the 1st part of the study, this deterioration was automatically shown as confirmed in the case of a transition to Part 2 regardless of the results of further surveys from Part 2. In contrast, this assumption of a confirmed deterioration was not made if patients were not included in Part 2 of the study. However, a significantly higher proportion of patients in the placebo arm had already transferred to Part 2 of the study at the time of the data cut-off. Accordingly, it cannot be ruled out that the results may be significantly biased to the detriment of the placebo arm. Against this background, the evaluations presented are considered to be unusable. An additional evaluation of the time until the first deterioration would have been desirable.

Health status EQ-5D VAS

In this study, the health status will be assessed using EQ-5D VAS. In the dossier, the pharmaceutical company presents evaluations up to the first confirmed deterioration by ≥ 10 points.

According to the comments on the survey of symptomology using EORTC QLQ-C30, the evaluations presented are not considered usable.

Quality of life

Data on disease-related quality of life are collected using EORTC QLQ-C30 function scales (global health status, physical function, role function, emotional function, cognitive function, and social function). The pharmaceutical company presented evaluations up to the first deterioration.

According to the comments on the survey of symptomology using EORTC QLQ-C30, the evaluations presented are not considered usable.

Side effects

Adverse events (AEs) in total

The results for the "the combined adverse events" endpoint are presented only on a supplementary basis.

In the pembrolizumab arm, 93.3% of patients suffered an adverse event; in the placebo arm, this was 90.2% of patients.

Serious adverse events (SAEs)

With regard to serious adverse events, there is a statistically significant difference to the detriment of pembrolizumab (HR: 1.56; [95% CI: 1.18; 2.06]; p = 0.002).

Adverse events (CTCAE grade ≥ 3)

In terms of adverse events (CTCAE grade ≥ 3), there is a statistically significant difference between pembrolizumab and placebo (HR: 1.66; [95% CI: 1.29; 2.14]; p < 0.001).

Discontinuation because of AEs

There is a statistically significant disadvantage to the detriment of pembrolizumab (HR: 3.78; [95% CI: 2.25; 6.34]; p value < 0.001).

Specific AEs

Immune-mediated AEs

A statistically significant difference to the disadvantage of pembrolizumab compared with the monitoring wait-and-see approach can be seen in the endpoints "immune-mediated AEs" (HR: 5.15; [95% CI: 3.63; 7.32]; p < 0,001), "Serious immune-mediated AEs" (HR: 14.00; [95% CI: 4.34; 45.15]; p < 0.001) and "Immune-mediated AEs (CTCAE grade ≥ 3; HR: 11.74; [95% CI: 3.62; 38.12]; p < 0.001).

With regard to the endpoint "immune-mediated AEs", there is an effect modification by the PD-L1 expression status. A statistically significant disadvantage results only for patients with positive PD-L1 expression status (HR: 6.30; [95% CI: 4.21; 9.43]; p < 0.001). Because no effect modification by this characteristic was found with respect to any other endpoint, this solitary effect is not considered further.

Other specific AEs

In detail, for the endpoints "Infections and infestations (SOC, AE)", "Skin and subcutaneous tissue disorders (SOC, AE)", "Xerostomia (PT, AE)", "Dyspepsia (PT, AE)", "Reduced appetite (PT, AE)", "Pain of the muscular and skeletal system (PT, AE)", "Dyspnoea (PT, AE)", "General disorders and administration site conditions (SOC, AE)", Gastrointestinal disorders (SOC, AE [CTCAE grade ≥ 3])", and "Respiratory, thoracic, and mediastinal disorders (SOC, AE [CTCAE grade ≥ 3]), there are only significant disadvantages to the detriment of pembrolizumab.

In the overall view, in the area of side effects, pembrolizumab has only disadvantages compared to a monitoring wait-and-see approach; these are considered relevant. These can be seen in an increase in AEs (CTCAE grade ≥ 3), serious AEs, and discontinuations because of AEs; if immune-mediated AEs, serious immune-mediated AEs, and immune-

mediated AEs (CTCAE grade ≥ 3) are considered alone as well as when considering all other specific side effects in detail.

Cross-endpoint consideration

In the present specific assessment situation, the G-BA does not disregard the following facts in its assessment of the results:

The patient population included in the KEYNOTE-054 study does not fully cover the patient population included in the therapeutic indication. Patients in Stage IIIA (according to AJCC 7) with lymph node metastases ≤ 1 mm and patients with in-transit or satellite metastases were not included.

For the study population included, there were clear advantages of therapy with pembrolizumab compared with a monitoring wait-and-see approach with regard to the occurrence of relapses.

At the same time, subgroup analyses showed no effect modification for the disease stage characteristic according to AJCC 7 for the endpoint relapse (1st data cut-off) and for the endpoint relapse-free survival.

Against the background of the data available and the statements of medical societies in the present and previous procedures in overlapping therapeutic indications, it is therefore considered medically plausible in the specific assessment situation to transfer the effects of Stage IIIA patients with lymph node metastases > 1 mm and patients without satellite or in-transit metastases to Stage IIIA patients with lymph node metastases ≤ 1mm and patients with satellite or in-transit metastases.

In summary, the statement on the additional benefit is therefore made for the entire population of patients in tumour stage III with lymph node involvement covered by the therapeutic indication under evaluation.

Overall assessment/conclusion

For the assessment of the additional benefit of pembrolizumab as monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection, data on morbidity, quality of life, and side effects are available. The benefit assessment is based on the results of the KEYNOTE-054 study in which pembrolizumab is compared to placebo. Based on the after-care strategy carried out in the study, this is seen as a sufficient approximation to the monitoring wait-and-see approach of the appropriate comparator therapy.

An evaluation of the endpoint overall survival was not planned for the data cut-offs presented.

In the category morbidity, statistically significant, clear advantages are shown in relation to the relapse rate and the relapse-free survival under pembrolizumab compared with a monitoring wait-and-see approach. The prevention of relapses is an essential therapeutic goal in the present curative therapy intent. However, because the observation period (21.6 months median) for the 2nd data cut-off is relatively short and not long enough to adequately reflect the high risk period for the occurrence of a relapse of 3 years after primary diagnosis, the extent of this benefit cannot be clearly quantified based on the data available. In this case, further data on the distribution of patient-individual observation durations would have been desirable for the assessment of this endpoint.

The evaluations on symptomology collected using EORTC QLQ-C30 and the health status measured using EQ-5D VAS presented by the pharmaceutical company are classified as unusable.

Correspondingly, the evaluations of the endpoint health-related quality of life collected using EORTC QLQ-C30 are also considered to be unusable.

In the side effects category, there are relevant disadvantages because of an increase in serious adverse events, adverse events (CTCAE grade ≥ 3), and discontinuations because of AEs. In detail, an increase in immune-mediated adverse events, serious immune-mediated adverse events and immune-mediated adverse events (CTCAE grade ≥ 3) was observed. Other specific AEs also showed only disadvantages.

In the overall view of the results for all available patient-relevant endpoints, the present adjuvant therapy situation has clear positive – but non-quantifiable – effects with regard to the prevention of relapses and relevant side effects. In addition, there are no data on overall survival and no reliable statements on symptomology and quality of life. The disadvantages in the side effects category are weighted against the background of the curative therapy claim. These do not call into question the advantages in preventing relapses.

For pembrolizumab as monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection, a non-quantifiable additional benefit has been identified.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of a randomised, double-blind, placebo-controlled study.

Because the benefit assessment is based on the results of only one study, at best indications of an additional benefit can be derived with regard to the reliability of data.

Across endpoints, the risk of bias is classified as low.

Overall, an indication is derived for the reliability of data of the additional benefit determined.

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 has 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 this case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a, paragraph 1 SGB V.

This resolution is based on the results of the currently ongoing KEYNOTE-054 study.

Because an evaluation of overall survival was not planned for the 1st data cut-off of 2 October 2017 nor for the 2nd data cut-off of 2 May 2018, no results are available for this endpoint. The benefit assessment for the endpoints relapses and relapse-free survival is based on the data cut-off of 2 May 2018. At that time, the observation period was not long enough to fully record the high-risk period for relapse. Accordingly, the data at this point in time are classified as not yet finally assessable.

The pharmaceutical company is required to submit final data on relapse-free survival, remote-metastasis-free survival, and overall survival to the European Medicines Agency (EMA) in the fourth quarter of 2023.

Because further clinical data from the KEYNOTE-054 study are expected to be relevant for assessing the benefits of the medicinal product, it is justified to limit the period of validity of the present resolution.

Conditions of the limitation

For the reassessment of pembrolizumab after expiry of the limitation period, the results from the KEYNOTE-054 study for all patient-relevant endpoints, in particular for overall survival and relapses, should be presented in the dossier.

A limitation of the resolution until 1 April 2024 is considered to be appropriate.

The G-BA is able, in principle, to revise the limitation if it has been presented with clear justification that it is insufficient or too long.

In accordance with Section 3, paragraph 1, number 5 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of pembrolizumab shall recommence when the limitation period has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the limitation period to prove the extent of the additional benefit of pembrolizumab (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5, Section 8, number 5 VerfO). The possibility that a benefit assessment of pembrolizumab can be carried out at an earlier point in time for other reasons (*cf* Chapter 5, Section 1 paragraph 2 VerfO) remains unaffected by this.

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment for the active ingredient pembrolizumab in a new therapeutic indication:

“KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.”

“A monitoring wait-and-see approach” was determined as an appropriate comparator therapy by the G-BA:

To assess the additional benefit, the pharmaceutical company presented the results of the randomized, double-blind KEYNOTE-054 study. In this study, pembrolizumab is compared with placebo, which, in connection with the investigation regime, is considered a sufficient approximation to a “Monitoring wait-and-see approach”.

Pembrolizumab shows a statistically significant, clear advantage in the prevention of relapse compared with a monitoring wait-and-see approach. The prevention of relapses is an essential therapeutic goal in the present curative therapy intent. However, because the observation period was too short, the extent of this advantage cannot be clearly quantified based on the data available.

Furthermore, there are no data available on overall survival and no reliable statements on symptomology and quality of life.

The advantages in terms of relapses are offset by relevant disadvantages in terms of side effects, in particular an increase in serious adverse events, adverse events (CTCAE grade ≥ 3) and discontinuations because of adverse events.

The disadvantages are weighted against the background of the curative therapy claim.

In the overall view, there is an indication of a non-quantifiable additional benefit.

Limitation of the resolution

The resolution is limited until 1 April 2024.

This resolution is based on the results of the ongoing KEYNOTE-054 study. Data on overall survival are not available for either of the two data cut-offs. At the time of the 2nd data cut-off, the observation period for the endpoints concerning relapse is not yet sufficiently long. Final data on relapse-free survival, remote metastasis-free survival, and overall survival must be submitted to the EMA by the end of 2023.

For the renewed benefit assessment of pembrolizumab after expiry of the limitation period, the results for all patient-relevant endpoints, in particular for overall survival and relapses, should be presented in the dossier.

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).

In the opinion of the G-BA, the patient numbers submitted by the pharmaceutical company in the present procedure do not represent a clearly better estimate compared with the determination of the patient numbers in the present therapeutic indication from the resolution on the benefit assessment for nivolumab of 21 February 2019. These are therefore used to calculate the number of patients. The approved therapeutic indication for nivolumab for the adjuvant treatment of melanoma includes disease stages III and IV and thus a larger patient population. Considering the patients in Stage III (3107 to 3955) and a SHI proportion of 85.9%, this results in approx. 2670–3400 patients. Uncertainties exist to the effect that this number also includes patients in tumour stage III without lymph node involvement.

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: 5 August 2019):

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

Treatment with pembrolizumab should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in skin and venereal diseases, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with melanomas.

According to the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the pharmaceutical company must provide the following information material on pembrolizumab:

- Training and information material for doctors/medical professionals
- Training and information material for the patient

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: 1 September 2019).

The recommended dosage for pembrolizumab in monotherapy is 200 mg every 3 weeks or 400 mg every 6 weeks. The three-week therapy scheme is used to calculate the costs.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year, even if the actual treatment duration is patient-individual and/or is shorter on average.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Pembrolizumab	1 x every 3 weeks	17	1	17
Appropriate comparator therapy				

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Monitoring wait-and-see approach	not quantifiable			

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Pembrolizumab	200 mg	200 mg	2 × 100 mg	17	17 × 200 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	not quantifiable				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail 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 pharmaceutical costs were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy wholesale 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 vial	€ 3,234.94	€ 1.77	€ 181.48	€ 3,051.69
Appropriate comparator therapy					
Monitoring wait-and-see approach	not quantifiable				

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 September 2019

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 standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services in accordance with Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic products of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 22 May 2018.

On 28 March 2019, 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 2 VerfO.

By letter dated 29 March 2019 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 27 June 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 July 2019. The deadline for submitting written statements was 22 July 2019.

The oral hearing was held on 5 August 2019.

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 were discussed at the session of the subcommittee on 10 September 2019, and the proposed resolution was approved.

At its session on 19 September 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	22 May 2018	Determination of the appropriate comparator therapy
Working group Section 35a	31 July 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 August 2019	Conduct of the oral hearing
Working group Section 35a	14 August 2019 21 August 2019 4 September 2019	Advice on the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG), evaluation of the written statement procedure
Subcommittee Medicinal product	10 September 2019	Concluding discussion of the proposed resolution
Plenum	19 September 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 19 September 2019

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

Prof Hecken