Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Pembrolizumab (new therapeutic indication: melanoma, adjuvant treatment, ≥ 12 years)

of 19 January 2023

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient pembrolizumab (Keytruda) 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 22 June 2022, pembrolizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 18 July 2022, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5,

Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication: "Keytruda as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and 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 November 2022 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 as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection**.**

Therapeutic indication of the resolution (resolution of 19.01.2023):

Keytruda as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB or IIC melanoma and who have undergone complete resection, and adolescents aged 12 years and older in tumour stage III after complete resection.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment

Appropriate comparator therapy for pembrolizumab as monotherapy:

- Monitoring wait-and-see approach

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

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to doctor's instructions

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

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

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

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

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

on 1. In addition to pembrolizumab, the following active ingredients are approved for the present therapeutic indication:

Dabrafenib, interferon alfa-2a[2], interferon alfa-2b[2], nivolumab and trametinib.

on 2. Adjuvant radiotherapy can be considered in principle in the present therapeutic indication.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Nivolumab: Resolution of 16 September 2021
- Pembrolizumab: Resolution of 19 September 2019
- Dabrafenib: Resolution of 22 March 2019
- Trametinib: Resolution of 22 March 2019

[2] Currently not sold in Germany.

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 indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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

For the present therapeutic indication, against the background that the corresponding treatment decision are influenced by the stage of the disease, it is considered appropriate to determine the appropriate comparator therapy differentiated according to the patient groups listed below.

Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection

Based on international guidelines, exclusive follow-up is a standard in the adjuvant disease setting of stage IIB or IIC melanoma. Adjuvant treatment with PD-1 inhibitors or MEK or BRAF inhibitors is explicitly not recommended for stage II melanoma.

Furthermore, according to the German S3 guideline, adjuvant interferon therapy should be offered in tumour stage IIB/C. The S3 guideline also points out that patients at high risk of metastasis can only be followed up.

The statements of the clinical experts in the present benefit assessment procedure showed that the use of interferon alfa in the adjuvant therapy of stage IIB/C melanoma is associated with only limited efficacy. Against the background of weighing up the benefits and side effects of such treatment, interferon alfa has only been used to a limited extent in the German healthcare context, according to clinical experts. According to clinical experts, it also had to be taken into account that interferon alfa was already only partially available in Germany in recent years. In recent years, the active ingredient interferon alfa has only been available in the form of individual medicinal preparations and predominantly only as a re-/parallel import. In addition, at the time of the resolution, all medicinal products with the active ingredient interferon alfa in the LAUER-TAXE® had now been reported out of circulation.

Against this background, interferon alfa cannot be considered as an appropriate comparator therapy.

As there is no evidence regarding non-medicinal treatment with adjuvant radiotherapy for stage II B/C, adjuvant radiotherapy is not considered as an appropriate comparator therapy.

According to the statements of clinical experts on the present benefit assessment procedure, there is no separate treatment standard for children and adolescents at this stage of the disease. The therapy of these patients is oriented towards the therapy of adults.
In this regard, the present guidelines do not provide any separate recommendations for the adjuvant treatment of adolescents aged 12 years and older with melanoma in tumour stage IIB or IIC after complete resection.

In the overall analysis, only monitoring wait-and-see approach is determined as the appropriate comparator therapy.

Adolescents aged 12 and over with melanoma in tumour stage III after complete resection

There is little evidence on treatment options for adjuvant treatment of adolescents aged 12 years and older with stage III tumours. The present guidelines on adjuvant treatment of melanoma in tumour stage III after complete resection do not contain any recommendations in this regard.

According to the assessments of the clinical experts produced in the written statement procedure for the present benefit assessment procedure, there is no separate treatment standard for children and adolescents at this stage of the disease. The therapy of these patients is oriented towards the therapy of adults.

Against this background, the treatment options for adults are used to determine the appropriate comparator therapy. In this regard, both the combination therapy dabrafenib in combination with trametinib and the anti-PD-1 antibodies nivolumab and pembrolizumab have found their way into the recommendations of the guidelines. Accordingly, the anti-PD-1 antibodies nivolumab and pembrolizumab are recommended for patients with BRAF wild type and both nivolumab and pembrolizumab as well as dabrafenib in combination with trametinib for patients with BRAF V600 mutation.

In the benefit assessment for the combination of dabrafenib and trametinib, which is only approved for patients with a BRAF V600 mutation, the G-BA found an indication of a major additional benefit compared to monitoring wait-and-see approach (resolution of 22 March 2019).

For nivolumab as monotherapy, the benefit assessment by the G-BA determined a hint for a major additional benefit compared to monitoring wait-and-see approach (resolution of 16 September 2021).

For pembrolizumab as monotherapy (in tumour stage III with lymph node involvement after complete resection in adults), the benefit assessment by the G-BA found an indication of a non-quantifiable additional benefit compared with monitoring wait-and-see approach (resolution of 19 September 2019). As the present benefit assessment is again an assessment of pembrolizumab as monotherapy (tumour stages IIB/C after complete resection in adults and adolescents aged 12 years and older and tumour stage III after complete resection in adolescents aged 12 years and older), pembrolizumab as monotherapy itself is not eligible as an appropriate comparator therapy.

As a non-medicinal treatment, adjuvant radiotherapy can, in principle, be considered in stage III. This serves to improve regional tumour control. Adjuvant radiotherapy is used on a patient-individual basis depending on the risk of recurrence and taking into account possible therapy-related side effects. There are no data demonstrating a positive impact of adjuvant radiotherapy on overall survival. A regular application cannot be derived, which is why adjuvant radiotherapy cannot be considered as an appropriate comparator therapy.

Overall, against this background, the following therapies are considered suitable comparators in the context of a clinical study:

- Dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection)
- Nivolumab.

These therapies, which are designated as suitable comparators, are not currently approved for the treatment of adolescents aged 12 years and older. There is a discrepancy between medicinal product approved in the indication and medicinal products used in health care.

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

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.

Change of the appropriate comparator therapy

Originally, the appropriate comparator therapy was determined as follows:

a) Adults with melanoma in tumour stage IIB or IIC after complete resection; adjuvant treatment

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to the doctor's instructions, taking into account interferon alfa and monitoring wait-and-see approach.

b) Adolescents 12 years and older with melanoma in tumour stage IIB or IIC after complete resection; adjuvant treatment

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to the doctor's instructions, taking into account interferon alfa and monitoring wait-and-see approach.

c) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

Appropriate comparator therapy for pembrolizumab as monotherapy:

Therapy according to doctor's instructions

Within the framework of the written statement procedure for the present benefit assessment procedure, the clinical experts explained that there is no separate treatment standard for children and adolescents in tumour stage IIB/C and that the therapy of these patients is oriented towards that of adults.

Furthermore, it emerged from the clinical experts' statements that the use of interferon alfa in the adjuvant therapy of stage IIB/C melanoma is associated with only limited efficacy. Against the background of weighing up the benefits and side effects of such treatment, interferon alfa has, according to clinical experts, only been used to a limited extent in the German healthcare context; the current treatment standard is therefore monitoring wait-and-see approach, both in adolescents aged 12 years and older and in adults. In addition, at the time of the resolution, all medicinal products with the active ingredient interferon alfa in the LAUER-TAXE® have now been reported out of circulation.

Taking into account the statements of the clinical experts, according to which the clinical picture and course are comparable, adults as well as adolescents aged 12 years and older with melanoma in tumour stage IIB or IIC after complete resection (adjuvant treatment) are

combined into one patient population. For the pooled patient population, only "monitoring wait-and-see approach" is determined as the appropriate comparator therapy.

This change in the appropriate comparator therapy means that the results of the KEYNOTE 716 study submitted by the pharmaceutical company in the dossier can be used for the present assessment. The KEYNOTE 716 study was presented additionally in IQWiG's dossier assessment. In addition, the results of the KEYNOTE 716 study were the subject of the statements, which is why the change in the appropriate comparator therapy does not necessitate a renewed conduct of the benefit assessment procedure.

2.1.3 Extent and probability of the additional benefit

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

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment

Indication of non-quantifiable additional benefit

Justification:

The present benefit assessment is the assessment of pembrolizumab as monotherapy for the adjuvant treatment of melanoma in tumour stages IIB or IIC in adults and adolescents aged 12 years and older, and in tumour stage III in adolescents aged 12 years and older as a result of an extension of the therapeutic indication. A benefit assessment on adults with stage III tumours has already been carried out by the G-BA in its resolution of 19 September 2019.

For the proof of additional benefit of pembrolizumab, the pharmaceutical company presented the results of the KEYNOTE 716 study.

KEYNOTE 716 is a multicentre, double-blind, randomised controlled trial comparing pembrolizumab and placebo in the adjuvant treatment of melanoma. The study included adolescents aged 12 years and older and adult patients who had undergone complete resection of a melanoma in tumour stages IIB or IIC (according to version 8 of the American Joint Committee on Cancer [AJCC] classification) within 12 weeks prior to randomisation. Beyond that, the patients were not allowed to have received any other treatment. The study included a total of only 1 subject under 18 years of age per treatment arm.

At the beginning of the study, patients were not allowed to have any indication of regional or remote metastatic disease. Furthermore, patients should have a good general health condition (for adults according to an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 or 1 or for children and adolescents according to a Lansky- or Karnofsky performance status ≥ 50) .

The 976 patients included were randomised 1:1 to treatment with pembrolizumab (N = 487) or placebo (N= 489).

Randomisation was stratified by T-classification of tumour stage according to AJCC version 8 (T3b [> 2.0-4.0 mm with ulceration] vs T4a [> 4.0 mm without ulceration] vs T4b [> 4.0 mm with ulceration]) as well as a separate stratum for adolescents aged 12 to 17 years.

The KEYNOTE 716 study consists of 2 parts, of which part 1 covers the initial adjuvant treatment and the subsequent observation period. In the event of a relapse, patients in both study arms have the option, under certain conditions, to cross over to part 2 of the study and be treated with pembrolizumab. Complete evaluations are available for Part 1 of the study. The present benefit assessment refers to the results from part 1 of the study.

Treatment was given in the KEYNOTE 716 study for 17 cycles of 3 weeks each. Particularly due to interruptions in therapy, this could result in treatment durations that exceed the maximum treatment duration of 1 year specified in the product information. The study report shows that 11% of patients in the pembrolizumab arm were treated for 1 year or longer, so that no relevant effects on the present benefit assessment are assumed.

Based on the study regime conducted in the KEYNOTE 716 study, the placebo comparison is considered to be a sufficient implementation of the appropriate comparator therapy "monitoring wait-and-see approach".

The KEYNOTE 716 study was conducted in 141 study sites across Africa, Asia, Australia, Europe, North America and South America. The study was launched in September 2018 and is currently ongoing.

For the benefit assessment, the 3rd data cut-off from 04.01.2022 was submitted. This is the 3rd planned interim analysis after 146 (planned) and 158 (occurred) events in the endpoint distant metastasis-free survival (DMFS). This data cut-off will be used for the present benefit assessment.

Extent and probability of the additional benefit

Mortality

In the KEYNOTE 716 study, no evaluations of overall survival were planned in the data cut-offs to date. No data on overall survival were submitted by the pharmaceutical company in the benefit assessment dossier. However, according to IQWiG's dossier assessment, information on the number of patients who deceased was available in the study report as part of the information on study conduct and patient flow. In IQWiG's dossier assessment, the data on deaths and the relative risk calculated from them were presented as overall mortality, which are used for the present benefit assessment.

No statistically significant difference was detected between the treatment arms based on these evaluations. Final analyses from the KEYNOTE 716 study on the endpoint of overall survival are pending.

Morbidity

Recurrences / Recurrence-free Survival (RFS)

Patients in the present therapeutic indication are treated with a curative therapeutic approach as part of the adjuvant treatment of melanoma after complete resection. Nevertheless, tumour cells might remain and cause a recurrence in the further course. Recurrence means that the attempt at a cure by the curative therapeutic approach was unsuccessful. The occurrence of a recurrence is patient-relevant.

The endpoints recurrence and RFS include the following individual components:
- local recurrence
- regional recurrence
- locoregional recurrence
- remote metastases
- joint occurrence of locoregional recurrence and remote metastases
- death without recurrence

The endpoint recurrence describes the percentage of patients with a recurrence event or death at the corresponding data cut-off (event rate). In the endpoint RFS, the time to the event (recurrence or death) is also considered (time-to-event analysis).

Recurrences (event rate)

For the endpoint recurrences, there was a statistically significant advantage of pembrolizumab versus placebo.

Recurrence-free survival (RFS)

Pembrolizumab results in a statistically significant prolongation of time to recurrence or death compared to placebo.

Overall, the endpoints recurrences and recurrence-free survival show a clear, clinically relevant advantage of pembrolizumab compared to monitoring wait-and-see approach.

However, as the observation period (approx. 27 months median) to the 04.01.2022 data cut-off is relatively short and not sufficiently long to adequately reflect the high-risk period for recurrence of 3 years after primary diagnosis, the magnitude of this benefit cannot be quantified with certainty based on the available data.

Symptomatology

Symptomatology is assessed in the KEYNOTE 716 study using the symptom scales of the disease-specific questionnaire EORTC QLQ-C30.

For this endpoint, the pharmaceutical company submitted continuous evaluations (mean differences compared to the start of the study) in the dossier for the benefit assessment.

For the endpoints fatigue, pain, dyspnoea, loss of appetite and diarrhoea, there was a statistically significant difference to the disadvantage of pembrolizumab. However, the respective 95% confidence interval of the standardised mean difference (SMD) was not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred, in each case, that the observed effect is relevant.

For all other endpoints, no statistically significant difference was detected between the study arms.

Thus, with regard to symptomatology, there are neither positive nor negative effects of pembrolizumab compared to the monitoring wait-and-see approach.

Health status

General health status is assessed in the KEYNOTE 716 study using the EQ-5D visual analogue scale (VAS).
For this endpoint, the pharmaceutical company submitted continuous evaluations (mean differences compared to the start of the study) in the dossier for the benefit assessment.

For the endpoint health status, there was a statistically significant difference to the disadvantage of pembrolizumab. The 95% confidence interval of the SMD was not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred that the observed effect is relevant.

Thus, there are neither positive nor negative effects of pembrolizumab with regard to the health status.

Quality of life

Health-related quality of life is assessed in the KEYNOTE 716 study using the functional scales of the disease-specific questionnaire EORTC QLQ-C30.

For this endpoint, the pharmaceutical company submitted continuous evaluations (mean differences compared to the start of the study) in the dossier for the benefit assessment.

For the endpoints global health status, role functioning and social functioning, there was a statistically significant difference to the disadvantage of pembrolizumab in each case. However, the respective 95% confidence interval of the standardised mean difference (SMD) was not completely outside the irrelevance range of -0.2 to 0.2. Thus, it cannot be inferred, in each case, that the observed effect is relevant.

For all other endpoints, no statistically significant difference was detected between the study arms.

With regard to health-related quality of life, there are therefore neither positive nor negative effects of pembrolizumab compared to monitoring wait-and-see approach.

Side effects

Adverse events (AEs)

In the KEYNOTE 716 study, AEs occurred in both study arms in almost all patients. The results were only presented additionally.

Serious adverse events (SAE)

For the serious adverse event, no statistically significant difference was detected between the treatment arms.

Severe AE (CTCAE grade ≥ 3)

For severe adverse events with CTCAE grade ≥ 3, there was a statistically significant difference to the disadvantage of pembrolizumab.

There was an effect modification due to the characteristic "age". For subjects > 65 years, there was a statistically significant difference to the disadvantage of pembrolizumab. For subjects ≤ 65 years, there was no statistically significant difference.

Discontinuation due to AEs

For the endpoint discontinuation due to AEs, there was a statistically significant difference to the disadvantage of pembrolizumab.

Specific AEs

For the specific AEs immune-mediated SAEs, immune-mediated severe AEs, endocrine disorders (SOC, severe AE), gastrointestinal disorders (SOC, severe AE), hepatobiliary disorders (SOC, severe AE), skin and subcutaneous tissue disorders (SOC, severe AE), there was a statistically significant difference to the disadvantage of pembrolizumab.

In summary, in terms of side effects, a disadvantage of treatment with pembrolizumab compared to monitoring wait-and-see approach can be identified due to the negative effects in severe AEs and therapy discontinuations due to AEs. With regard to specific adverse events, there were disadvantages for pembrolizumab in detail.

Overall assessment

For the assessment of the additional benefit of pembrolizumab for adjuvant treatment in adults and adolescents aged 12 years and older with melanoma in tumour stage IIB or IIC after complete resection, data on mortality, morbidity, quality of life and side effects are available. The benefit assessment is based on the results of the double-blind, randomised controlled KEYNOTE 716 study, which compared pembrolizumab with placebo. Based on the study's investigation regime in after-care, this is considered sufficient implementation of the appropriate comparator therapy "monitoring wait-and-see approach".

Based on evaluations of overall mortality, there is no statistically significant difference between the treatment arms. Final analyses from the KEYNOTE 716 study on the endpoint of overall survival are pending.

With regard to recurrence rate and recurrence-free survival, there are statistically significant, clear advantages of pembrolizumab over monitoring wait-and-see approach. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting. However, as the observation period (approx. 27 months median) to the 04.01.2022 data cut-off is not sufficiently long to adequately reflect the high-risk period for recurrence of 3 years after primary diagnosis, the extent of this benefit cannot be quantified with certainty based on the available data.

There were neither positive nor negative effects with regard to symptomatology (assessed using the EORTC QLQ-C30) and health status (assessed using the EQ-5D VAS).

For health-related quality of life (assessed by EORTC QLQ-C30), there were also neither positive nor negative effects.

In terms of side effects, there are disadvantages of pembrolizumab for severe AEs and therapy discontinuations due to AEs. There were no statistically significant differences between the study arms in terms of serious AE. In detail, the specific AEs show disadvantages for pembrolizumab.

In the overall view of the results, in the present adjuvant treatment setting there are clear positive effects, the extent of which, however, cannot be quantified with certainty, with regard to the avoidance of recurrences, in contrast to relevant disadvantages with regard to side effects. There are no differences between the study arms with regard to overall mortality, symptomatology, health status and quality of life. The disadvantages in terms of side effects are weighted against the background of the present curative therapy claim. These do not question the advantage in avoiding recurrences.
Overall, a non-quantifiable additional benefit is found for pembrolizumab compared to monitoring wait-and-see approach.

Reliability of data (probability of additional benefit)

The present assessment is based on the results of the randomised, double-blind, controlled phase III KEYNOTE 716 study. At the study level, the risk of bias is considered low.

For the endpoints overall mortality and recurrence, there is also a low risk of bias.
For the endpoints in the areas of symptomatology, health status and health-related quality of life, the risk of bias is classified as high due to the decreasing response to questionnaires in the course of the study.

Due to the known side effect profile of pembrolizumab in comparison to placebo, limitations in blinding and therefore a tendency towards increased risk of bias are assumed for the endpoints on side effects.

Overall, the available data basis is subject to uncertainties. However, these uncertainties are not rated to be so high as to justify a downgrading of the reliability of data of the overall assessment. Thus, the reliability of data for the additional benefit determined is classified in the category "indication".

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

For the adjuvant treatment of adolescents aged 12 years and older with melanoma in tumour stage III after complete resection, an additional benefit is not proven.

Justification:

For adolescents aged 12 years and older with stage III melanoma after complete resection, no data were presented for the assessment of the additional benefit of pembrolizumab compared with the appropriate comparator therapy. In the KEYNOTE 716 study, only patients with tumour stage IIB or IIC were examined.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab:

"Keytruda as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection."

Only adults and adolescents aged 12 years and older in tumour stages IIB or IIC after complete resection as well as adolescents aged 12 years and older in tumour stage III after complete resection are considered here. The benefit assessment on adults with stage III tumours was carried out with the resolution of 19 September 2019.

In the therapeutic indication to be considered, 2 patient groups were distinguished:
a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment
b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

Patient group a)

The G-BA determined the "monitoring wait-and-see approach" as the appropriate comparator therapy.

Results from the double-blind RCT KEYNOTE 716 are available for the assessment. In this study, pembrolizumab is compared to placebo, which is considered to be sufficient implementation of the appropriate comparator therapy based on the after-care conducted in the study.

No statistically significant difference was detected between the treatment arms regarding overall mortality.

In the endpoint category morbidity, pembrolizumab showed significant advantages compared to the monitoring wait-and-see approach in terms of recurrence rate and recurrence-free survival. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting. However, due to a too short observation period, the extent of this advantage cannot be quantified with certainty based on the available data.

There were neither positive nor negative effects on symptomatology, health status or health-related quality of life.

In terms of side effects, the disadvantages of pembrolizumab can be seen in severe AEs, therapy discontinuations due to AEs and, in detail, in specific AEs.

Overall, clear positive effects in the avoidance of recurrences, the extent of their effect cannot be quantified with certainty, are set against relevant disadvantages in terms of side effects. The disadvantages in terms of side effects are weighted against the background of the present curative therapy claim. These do not question the advantage in avoiding recurrences.

Overall, the data basis is subject to uncertainties, which, however, are not determined to be so high as to justify a downgrading of the reliability of data.

As a result, an indication of a non-quantifiable additional benefit is found for pembrolizumab compared to monitoring wait-and-see approach.

Patient group b)

The appropriate comparator therapy was determined by G-BA to be a "therapy according to doctor's instructions".

For adolescents aged 12 years and older with stage III melanoma after complete resection, no data were presented for the assessment of the additional benefit of pembrolizumab compared with the appropriate comparator therapy. In the KEYNOTE 716 study, only patients with tumour stage IIB or IIC were examined. As a result, an additional benefit of pembrolizumab in this patient group is not proven.

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

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

The G-BA bases the resolution for patient group a) on the figures from IQWiG's dossier assessment, which were calculated on the basis of the information in the pharmaceutical company's dossier. For patient group b), the data from the dossier of the pharmaceutical company are used. It should be noted that the number of children and adolescents in the SHI target population may be slightly higher because the prognosis for children and adolescents aged 12 to 17 years with melanoma is too low.

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: 3 January 2023):

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 melanoma, as well as specialists in skin and sexually transmitted diseases, and specialists in paediatrics and adolescent medicine with specialisation in paediatric haematology and oncology, and other specialists participating in the Oncology Agreement.

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

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2023).

Treatment period:

The maximum duration of treatment with pembrolizumab is stated in the product information as one year, but may be shorter for individual patients.
Against this background, therefore, only the completed cycles in the treatment year are considered.

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Adults				
Pembrolizumab	1 x every 21 days	17.4	1	17
	or			
	1 x every 42 days	8.7	1	8
Adolescents from 12 years				
Pembrolizumab	1 x every 21 days	17.4	1	17
Appropriate comparator therapy				
Monitoring wait-and-see approach	incalculable			

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Pembrolizumab	1 x every 21 days	17.4	1	17
Appropriate comparator therapy				
Therapy according to doctor's instructions[3]	No data available			

Consumption:

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

According to the product information for pembrolizumab, the dosage in adults is either 200 mg every 21 days or 400 mg every 42 days. The dosage in adolescents 12 years and older with melanoma is 2 mg per kg body weight, up to a maximum of 200 mg every 21 days.

[3] The treatment options dabrafenib in combination with trametinib (only for patients with BRAF V600 mutation-positive melanoma in tumour stage III after complete resection) and nivolumab are suitable comparators for the present benefit assessment in the context of therapy according to doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication, and therefore, no costs are presented for these medicinal products.

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. For body weight, a range between 47.1 kg for 12-year-olds and 67.0 kg for 17-year-olds is therefore assumed according to the official representative statistics "Microcensus 2017"[4].

a) Adults and adolescents aged 12 years and older with melanoma in tumour Stage IIB or IIC after complete resection; adjuvant treatment

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					
Adults					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17	34 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8	32 x 100 mg
Adolescents from 12 years					
Pembrolizumab	2 mg/ kg = 94.2 mg - 2 mg /kg = 134 mg	94.2 mg - 134 mg	1 x 100 mg - 2 x 100 mg	17	17 x 100 mg - 34 x 100 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	incalculable				

b) Adolescents aged 12 years and older with melanoma in tumour stage III after complete resection; adjuvant treatment

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pembrolizumab	2 mg/ kg = 94.2 mg - 2 mg /kg = 134 mg	94.2 mg - 134 mg	1 x 100 mg - 2 x 100 mg	17	17 x 100 mg - 34 x 100 mg

[4] Information system of federal health reporting, average body measurements of the population (height in m, weight in kg). Characteristics of classification: Years, Germany, age, sex [online]. URL: https://www.gbe-bund.de/gbe/pkg_isgbe5.prc_menu_olap?p_uid=gast&p_aid=42472020&p_sprache=D&p_help=3&p_indnr=223&p_indsp=&p_ityp=H&p_fid=

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Therapy according to doctor's instructions[3]	No data available				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Pembrolizumab 100 mg	1 CIS	€ 2,974.79	€ 1.77	€ 285.60	€ 2,687.42
Appropriate comparator therapy					
Monitoring wait-and-see approach	incalculable				
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g., regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Pembrolizumab

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

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

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

3. Bureaucratic costs calculation

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

4. Process sequence

At its sessions on 27 July 2021 and 12 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 July 2022.

On 18 July 2022, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 25 July 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 October 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 November 2022. The deadline for submitting written statements was 22 November 2022.

The oral hearing was held on 5 December 2022.

On 6 December 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 6 December 2022 replaces version 1.0 of the dossier assessment dated 28 October 2022. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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 10 January 2023, and the proposed resolution was approved.

At its session on 19 January 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 October 2021 and 27 July 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	12 July 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	29 November 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	5 December 2022	Conduct of the oral hearing
Working group Section 35a	13 December 2022 3 January 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	10 January 2023	Concluding discussion of the draft resolution
Plenum	19 January 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 19 January 2023

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

Prof. Hecken