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: renal cell carcinoma, adjuvant treatment, monotherapy, pretreated patients)

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 11 November 2021, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for pembrolizumab, among other indications, in the indication "for the adjuvant treatment of renal cell carcinoma with increased risk of recurrence after nephrectomy or after nephrectomy and resection of metastatic lesions" in accordance with Section 35a paragraph 5b SGB V. The pharmaceutical company expected marketing authorisation extensions for the active ingredient pembrolizumab within the period specified in Section 35a paragraph 5b SGB V for several therapeutic indications at different times.

In its session on 6 January 2022, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment

and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the last therapeutic indication of the therapeutic indications covered by the application, at the latest six months after the first relevant date. All marketing authorisations for the therapeutic indications covered by the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

For the therapeutic indication in question here, "adjuvant treatment of renal cell carcinoma with increased risk of recurrence after nephrectomy or after nephrectomy and resection of metastatic lesions", pembrolizumab received the extension of the marketing authorisation as a major type 2 variation as defined according to Annex 2 No. 2a 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, 12.12.2008, p. 7) on 24 January 2022. In accordance with the resolution of 6 January 2022, the benefit assessment of the active ingredient pembrolizumab in this new therapeutic indication thus began at the latest within four weeks, i.e., at the latest on 20 July 2022, after the last approval, which took place on 22 June 2022, of pembrolizumab in the therapeutic indications for the treatment of "melanoma in patients aged 12 years and older".

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

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

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

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

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

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

Therapeutic indication of the resolution (resolution of 19.01.2023):

See therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with renal cell carcinoma at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions; adjuvant treatment

Appropriate comparator therapy for pembrolizumab as monotherapy:

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 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. No other approved medicinal products besides pembrolizumab could be identified for the present therapeutic indication. In accordance with the present therapeutic indication, medicinal products with explicit marketing authorisation for advanced/metastatic renal cell carcinoma and for exclusively palliative use have not been considered.

on 2. As a non-medicinal therapy option, radiotherapy would in principle be conceivable in the present therapeutic indication. However, there are no recommendations on this in the evidence considered, which is why radiotherapy was not determined as an appropriate comparator therapy.

on 3. The following resolutions on the applications of medicinal products are available:

Annex VI to Section K of the Pharmaceuticals Directive - Prescribability of approved medicinal products in non-approved therapeutic indications; Part B: Active ingredients that are not prescribable in off-label uses (last revised: October 2022):

- Inhaled interleukin-2 (Proleukin®) for the treatment of renal cell carcinoma (not prescribable)

on 4. The general state of medical knowledge, on which the finding of the G-BA is based, was illustrated by systematic research for guidelines as well as reviews of clinical studies in the present therapeutic indication and can be found in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V", which was sent to the pharmaceutical company.

Based on the available evidence, no recommendations for active therapy can be derived with regard to adjuvant treatment of renal cell carcinoma. So far, there is no evidence for the benefit of adjuvant therapy in the present treatment setting. Results of phase III studies with targeted therapies have so far shown no improvement in overall survival compared to placebo, but have been associated with high toxicity.

Based on the fact that patients in the present therapeutic indication do not receive a specific therapy according to the current state of medical knowledge, a monitoring wait-and-see approach represents the appropriate comparator therapy.

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.

2.1.3 Extent and probability of the additional benefit

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

Hint for a minor additional benefit

Justification:

The benefit assessment is based on the results of the randomised, double-blind, placebo-controlled phase III KEYNOTE 564 study. The studies compared pembrolizumab versus placebo. The investigations carried out in the placebo arm largely correspond to the recommendations of the S3 guideline[2] and are assessed as sufficient implementation of the appropriate comparator therapy consisting of the monitoring wait-and-see approach.

Adults with clear cell renal cell carcinoma and increased risk of recurrence after partial nephroprotective or total nephrectomy (with complete resection of metastatic lesions) and negative surgical margins were included. Increased risk of recurrence was defined as

[2] Guideline programme in oncology. S3 Guideline - Diagnosis, therapy and after-care of renal cell carcinoma (long version 3.0), 2021

intermediate-high or high risk of recurrence or M1 status with no evidence of disease (NED)[3]. A total of 994 patients were randomised in a 1:1 ratio to the two treatment arms (test arm: N = 496, control arm: N = 498). Stratification was done according to the characteristic metastasis status (M1 NED vs M0). Within M0, additional stratification was done according to ECOG-PS (0 vs 1) and region (USA vs non-USA).

Patients must not have received systemic therapy for the treatment of advanced renal cell carcinoma and should be in good general health condition according to the Eastern Cooperative Oncology Group - Performance Status (ECOG-PS) ≤ 1. Patient characteristics were balanced between the two study arms. The patients were on average about 58 years old, predominantly male (70 % vs 72 %) and had an ECOG-PS of 0 (about 85 %).

The treatment with pembrolizumab was carried out according to the requirements in the product information. Patients were treated for up to 1 year (maximum 17 cycles) or until recurrence, unacceptable toxicity or therapy discontinuation for other reasons was confirmed.

The KEYNOTE 564 study was launched in June 2017 and is currently ongoing. It was conducted at 212 study sites in 21 countries in Europe, North and South America, Asia and Australia, with the majority of patients enrolled in the European Union (38%) or North America (about 26%).

Currently, two data cut-offs are available. The data cut-off from 14 December 2020 is a primary analysis specified a priori for the primary endpoint of disease-free survival (DFS) and the interim analysis of the endpoint overall survival. In addition, results on patient-relevant endpoints in the categories of morbidity, quality of life and side effects are available for this data cut-off. The rationale for conducting the second data cut-off on 14 July 2021 was unclear based on the information in the dossier. In the written statement procedure, the pharmaceutical company stated that the 2nd data cut-off was requested by the EMA. Evaluations of the endpoints of mortality, morbidity and side effects are available for this data cut-off. However, patient-reported endpoints (PROs) in the morbidity and quality of life category are only available for the 1st data cut-off from 14 December 2020. For the present benefit assessment, the results of the 1st data cut-off of 14 December 2020 are used, as it is assumed that as of 2nd data cut-off, no additional gain in knowledge is to be expected. For all other patient-relevant endpoints, the results from the 2nd data cut-off from 14 July 2021 are used.

[3] Intermediate-high risk was defined as pT2 with grade 4 or sarcomatoid characteristics or as pT3 of any grade; each without lymph node involvement (N0) and without remote metastases (M0). High risk was defined as pT4 of any grade with N0 and M0 or pT of any stage, with any grade and with lymph node involvement (N1) and M0. M1-NED-RCC status included patients who had solid, isolated soft tissue metastases that could be completely resected either at the time of nephrectomy (synchronous) or ≤ 1 year after nephrectomy (metachronous).

Extent and probability of the additional benefit

Mortality

Overall survival

Overall survival was defined in the KEYNOTE 564 study as the time from randomisation to death, regardless of the underlying cause.

For the endpoint of overall survival, there is a statistically significant advantage of pembrolizumab versus the monitoring wait-and-see approach.

For the assessment of the data on overall survival, it must be taken into account that in a relevant proportion of patients with recurrence, no systemic subsequent therapy was carried out or no treatment with an immune checkpoint inhibitor took place.

The German S3 guideline[4] recommends first-line treatment with an immune checkpoint inhibitor for patients with advanced or metastatic clear cell renal cell carcinoma, regardless of the risk profile: Combination pembrolizumab or avelumab each plus axitinib; for intermediate or poor risk, the combination pembrolizumab plus ipilimumab.

In the dossier, the pharmaceutical company submits information on subsequent therapies (systemic therapies, operations performed and radiotherapy), which he considers to be the 1st subsequent therapy after the occurrence of a recurrence. In addition, he submits with his statement information on the 1st subsequent therapy, which, however, differ from the data submitted in the dossier. Since in some cases fewer patients received a specific subsequent therapy in the afterwards submitted evaluations, it is assumed that the data from the dossier are the data on all subsequent therapies and the afterwards submitted data are the data on the 1st subsequent therapy.

In the comparator arm of the KEYNOTE 564 study, only just under 20% of patients with recurrence who had not died received immune checkpoint inhibitor-based therapy and about 35% of patients with recurrence received VEGF / VEGFR-targeted therapy as 1st subsequent therapy. In terms of all subsequent therapies, approximately 30% of patients with recurrence received immune checkpoint inhibitor-based therapy and 51% received VEGF/ VEGFR-targeted therapy. In terms of subsequent therapies, a large proportion of the patients in the comparator arm of the KEYNOTE 564 study were not treated according to the recommendations of the German S3 guideline.

Against the background of the statements of the scientific-medical societies on the assessment of the subsequent therapies, the G-BA nevertheless considers the data on overall survival to be sufficiently interpretable and uses them for the present assessment.

Taking into account the short observation period and the small number of events that occurred, as well as the remaining uncertainties regarding subsequent therapies, it is concluded that the extent of improvement in overall survival cannot be quantified with certainty.

[4] Guideline programme in oncology. S3 guideline - Diagnostics, therapy and after-care of renal cell carcinoma (long version 3.0) [online]. 2021

Morbidity

Recurrences

The endpoint recurrence is a composite endpoint and includes the components local recurrence, remote metastases and death from any cause. For the endpoint recurrence, the results of the operationalisations are presented as the percentage of patients with recurrence (recurrence rate) and as disease-free survival.

Patients in the present therapeutic indication are treated with a curative therapeutic approach as part of the adjuvant treatment of renal cell carcinoma after partial nephroprotective or complete nephrectomy (with a complete resection of metastatic lesions) and negative surgical margins. 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 pharmaceutical company submits evaluations based on the principal investigator's assessment and, as a sensitivity analysis, evaluations based on a blinded, central and independent committee (BICR).

There is a statistically significant difference between the treatment groups for both recurrence rates and disease-free survival according to the principal investigator's assessment for the advantage of pembrolizumab over the monitoring wait-and-see approach.

For the endpoint recurrences, operationalised as disease-free survival, there is also an effect modification by the characteristic metastasis status (M0 vs M1 NED), whereby a clear advantage of pembrolizumab is found for patients with metastasis status M0 and a very clear advantage for patients with metastasis status M1 NED compared to the monitoring wait-and-see approach. For the endpoint recurrence operationalised as recurrence rate, no effect modification is available.

The operationalisations according to BICR, presented additionally, show a statistically significant difference between the treatment groups for disease-free survival, event rate and event-free survival to the advantage of pembrolizumab compared to the monitoring wait-and-see approach. For recurrence rates, there is no statistically significant difference between the treatment groups.

In principle, in the present situation, a comparison of active ingredient versus placebo, the operationalisation according to BICR is the appropriate evaluation method, in particular due to the side effect profile of pembrolizumab and a resulting possible unblinding of the medical investigators. However, in the present case, the assessment of recurrences by imaging was stopped during the course of the study as soon as the medical investigators detected a recurrence. In these cases, it was therefore not possible for the BICR to verify and possibly make a different assessment, so that the data may be incomplete. This results in uncertainties in the interpretation of these data.

Overall, for the endpoint of recurrences, operationalised as recurrence rates and disease-free survival, there is a clear advantage for pembrolizumab over monitoring wait-and-see approach, but this is subject to uncertainty.

Symptomatology

Symptomatology was assessed in the KEYNOTE 564 study using FKSI-DRS and EORTC QLQ-C30. The pharmaceutical company submitted evaluations of the mean change compared to the start of the study (MMRM analyses) as of the 1st data cut-off from 14 December 2020. The endpoints were collected until the occurrence of a recurrence or the start of oncological subsequent therapy.

For the endpoint symptomatology assessed by the FKSI-DRS, the evaluation based on mean differences shows a statistically significant difference between the treatment groups. However, it cannot be inferred from the results that the observed effect is relevant, as the 95 % CI of the SMD is not completely outside the irrelevance range of -0.2 to 0.2 in each case.

For the symptomatology assessed by EORTC QLQ-C30, statistically significant differences between the treatment groups were found for the endpoints exhaustion, nausea and vomiting, dyspnoea and loss of appetite in the evaluations based on mean differences. However, it cannot be inferred from the results that the observed effect is relevant, as the 95 % CI of the SMD is not completely outside the irrelevance range of -0.2 to 0.2 in each case. For the endpoints pain, insomnia, constipation and diarrhoea, the evaluations based on mean differences show no statistically significant differences between the treatment groups.

For the endpoints symptomatology assessed by FKSI-DRS and symptomatology assessed by EORTC QLQ-C30, there were neither advantages nor disadvantages for pembrolizumab compared to the monitoring wait-and-see approach.

Health status

The health status is assessed in the KEYNOTE 564 study using the EQ-5D visual analogue scale (VAS). The pharmaceutical company submitted evaluations of the mean change from the start of the study (MMRM analyses). The endpoint was collected until the occurrence of a recurrence or the start of oncological subsequent therapy.

For the endpoint health status, assessed by EQ-5D VAS, there was no statistically significant difference between the treatment groups in the evaluation based on mean differences.

In the overall assessment of the endpoint category morbidity, there is a clear advantage for pembrolizumab in the endpoint recurrences compared to the monitoring wait-and-see approach, which is, however, subject to uncertainties.

Quality of life

Health-related quality of life was assessed in the KEYNOTE 564 study using the EORTC QLQ-C30. The pharmaceutical company submitted evaluations of the mean change from the start of the study (MMRM analyses). The endpoints were collected until the occurrence of a recurrence or the start of oncological subsequent therapy.

For health-related quality of life, no statistically significant differences between the treatment groups were found for the endpoints global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning in the evaluations based on mean differences.

Thus, for the endpoint category health-related quality of life, there are no advantages or disadvantages of pembrolizumab compared to the monitoring wait-and-see approach.

Side effects

Adverse events (AEs) in total

AEs occurred in all study participants. The results were only presented additionally.

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

For the endpoints SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, there was a statistically significant difference between the treatment groups to the disadvantage of pembrolizumab compared to the monitoring wait-and-see approach.

This disadvantage is rated as moderate for the endpoints SAEs and severe AEs (CTCAE grade ≥ 3) and as significant for discontinuation due to AEs.

For severe AEs (CTCAE grade ≥ 3), an effect modification by the characteristic "age" is shown. For subjects < 65 years of age, there is a statistically significant difference to the disadvantage of pembrolizumab. For subjects ≥ 65 years, there was no statistically significant difference.

Specific AEs

For the endpoints of immune-mediated SAEs and immune-mediated severe AEs, there was a statistically significant difference between the treatment groups to the disadvantage of pembrolizumab compared to the monitoring wait-and-see approach.

In addition, for the endpoints endocrine disorders (severe AEs), skin and subcutaneous tissue disorders (severe AEs), gastrointestinal disorders (severe AEs), investigations (severe AEs) and metabolism and nutrition disorders (severe AEs), there is a statistically significant difference between the treatment groups to the disadvantage of pembrolizumab compared to the monitoring wait-and-see approach.

The overall results on side effects show moderate differences in the endpoints SAEs and severe AEs (CTCAE grade ≥ 3) as well as clear differences in treatment discontinuations due to AEs between the treatment arms to the disadvantage of pembrolizumab versus the monitoring wait-and-see approach. In detail, disadvantages can be seen in immune-mediated SAEs and immune-mediated AEs, among others.

Subgroup analyses on metastasis status (M0 vs M1 NED)

For the characteristic metastasis status (M0 vs M1 NED), there is an effect modification for the endpoint recurrences, operationalised as disease-free survival. Subgroup analyses for this characteristic for all other patient-relevant endpoints (overall survival, recurrence rates, symptomatology, health status, health-related quality of life and the endpoints of side effects) are not available in the dossier and were also not subsequently submitted in the written statement procedure. This is viewed critically by the G-BA, as it is unclear to what extent the effect modification for the characteristic metastasis status in disease-free survival has an impact on the other patient-relevant endpoints, in particular side effects.

Overall assessment

For the assessment of the additional benefit of pembrolizumab as monotherapy for the adjuvant treatment of adults with renal cell carcinoma who are at increased risk of recurrence after nephrectomy or after nephrectomy and resection of metastatic lesions, results on mortality, morbidity, quality of life and side effects are available from the double-blind randomised controlled KEYNOTE 564 study. The study, which is still ongoing, compares pembrolizumab to placebo. The investigations carried out in the placebo arm in the study

largely correspond to the recommendations of the S3 guideline[5] and are evaluated as sufficient implementation of the appropriate comparator therapy (monitoring wait-and-see approach).

For the endpoint of overall survival, there is a statistically significant difference to the advantage of pembrolizumab compared to the monitoring wait-and-see approach. However, the extent of the improvement cannot be quantified with certainty, taking into account the short observation periods and the few events that occurred.

In the overall consideration of the results on morbidity, there is a clear advantage of pembrolizumab in the endpoint of recurrences, which, however, is subject to uncertainties. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

For the patient-reported endpoints in the categories morbidity (assessed by FKSI-DRS, EORTC QLQ-C30 and EQ-5D VAS) and health-related quality of life (assessed by EORTC QLQ-C30), there were no advantages or disadvantages for pembrolizumab compared to the monitoring wait-and-see approach.

In the endpoint category of side effects, there were moderate differences in the endpoints SAE and severe AEs (CTCAE grade ≥ 3) as well as clear differences in treatment discontinuations due to AEs between the treatment arms to the disadvantage of pembrolizumab versus the monitoring wait-and-see approach. In detail, disadvantages can be seen in immune-mediated SAEs and immune-mediated AEs, among others.

Overall, the advantages - improvement in overall survival and avoidance of recurrences - are offset by relevant disadvantages in terms of side effects, which also led to a significant increase in therapy discontinuations due to AEs in the study.

In a weighing decision, the G-BA comes to the conclusion that the advantages of treatment with pembrolizumab, in particular the clear advantage in the avoidance of recurrences, clearly outweigh the disadvantages in terms of side effects. However, even taking into account limitations in the assessment of the extent of improvement in overall survival and recurrences, the finding of an overall major additional benefit does not appear justified on the basis of the available data. Thus, pembrolizumab is found to have a minor additional benefit compared to the 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, phase III KEYNOTE 564 study.

At the study level, the risk of bias is considered low.

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.

[5] Guideline programme in oncology. S3 Guideline - Diagnosis, therapy and after-care of renal cell carcinoma (long version 3.0), 2021

A relevant uncertainty arises from the fact that subgroup analyses for the characteristic metastasis status (M0 vs M1 NED) are not available for all patient-relevant endpoints, but only for the primary endpoint DFS. In this respect, it is unclear to what extent the effect modification of the endpoint DFS due to the characteristic metastasis status also affects other patient-relevant endpoints, in particular the side effects.

Uncertainties arise for the endpoint recurrences due to the available operationalisation: The results of the analyses according to the principal investigator differ in comparison to the analysis according to BICR. During the evaluations according to the principal investigator, the medical investigators may be unblinded due to the side effect profile of pembrolizumab. The analyses according to BICR may be incomplete because the assessment of recurrences by imaging was terminated as soon as the medical investigators detected a recurrence.

In summary, the G-BA deduces a hint for the identified additional benefit with regard to the reliability of data (probability of additional benefit).

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab as monotherapy for the adjuvant treatment of adults with renal cell carcinoma who are at increased risk of recurrence after nephrectomy or after nephrectomy and resection of metastatic lesions.

The monitoring wait-and-see approach was determined as the appropriate comparator therapy.

For the proof of an additional benefit, results from the double-blind, randomised controlled KEYNOTE 564 study were presented for the endpoint categories mortality, morbidity, quality of life and side effects.

For the endpoint of overall survival, there is a statistically significant difference to the advantage of pembrolizumab compared to the monitoring wait-and-see approach. However, the extent of the improvement cannot be quantified with certainty, taking into account the short observation periods and the few events that occurred.

In the overall consideration of the results on morbidity, there is a clear advantage of pembrolizumab in the endpoint of recurrences, which, however, is subject to uncertainties. The avoidance of recurrences is an essential therapeutic goal in the present curative treatment setting.

For the patient-reported endpoints in the categories of morbidity and quality of life, there are no advantages or disadvantages for pembrolizumab compared to the monitoring wait-and-see approach.

In the endpoint category of side effects, there were moderate differences in the endpoints SAE and severe AEs (CTCAE grade ≥ 3) as well as clear differences in treatment discontinuations due to AEs between the treatment arms to the disadvantage of pembrolizumab versus the monitoring wait-and-see approach. In detail, disadvantages can be seen in immune-mediated SAEs and immune-mediated AEs, among others.

Overall, the advantages - improvement in overall survival and avoidance of recurrences - are offset by relevant disadvantages in terms of side effects, which also led to a significant increase in therapy discontinuations due to AEs in the study.

In a weighing decision, the G-BA comes to the conclusion that the advantages of treatment with pembrolizumab, in particular the clear advantage in the avoidance of recurrences, clearly outweigh the disadvantages in terms of side effects. However, even taking into account limitations in the assessment of the extent of improvement in overall survival and recurrences, the finding of an overall major additional benefit does not appear justified on the basis of the available data.

The reliability of data is rated as a hint, in particular due to the lack of subgroup analyses and uncertainties in the endpoint recurrences.

In summary, a hint for a minor additional benefit of pembrolizumab compared with the monitoring wait-and-see approach is found.

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

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

The G-BA bases its resolution on the patient numbers stated by the pharmaceutical company. The number of patients in the SHI target population determined by the pharmaceutical company is expected to be in the range of the upper limit. It may also be higher, as patients with an earlier stage at initial diagnosis and a nephrectomy in the course of the disease were not taken into account.

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 as well as specialists in internal medicine and nephrology and other specialists participating in the Oncology Agreement, all of whom are experienced in the treatment of patients with renal cell carcinoma.

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).

The maximum treatment duration for adjuvant treatment with pembrolizumab is given as one year, but may be shorter on a patient-individual basis.

Against this background, therefore, only the completed cycles in the treatment year are considered.

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 per 21-day cycle	17.4	1	17
	or			
	1 x per 42-day cycle	8.7	1	8
Appropriate comparator therapy				
Monitoring wait-and-see approach	incalculable			

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 in monotherapy, the dosage in adults is either 200 mg every 21 days or 400 mg every 42 days.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Pembrolizumab	200 mg	200 mg	2 x 100 mg	17	34 x 100 mg
	or				
	400 mg	400 mg	4 x 100 mg	8	32 x 100 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Monitoring wait-and-see approach	incalculable				

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	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					

LAUER-TAXE® last revised: 01 January 2023

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 session on 12 June 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

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 2, number 5 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.

By letter dated 6 December 2022, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 29 December 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 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 June 2019	Determination 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 / 6 December 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
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