Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Pembrolizumab (New Therapeutic Indication: Renal Cell Carcinoma, First-Line, Combination with Axitinib)

of 14 May 2020

Contents

1. Legal basis

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

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

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

According to Section 35a, paragraph 3 SGB V, the G-BA 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 26 August 2019, pembrolizumab received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2, number 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 December 2008, p. 7).

On 13 May 2019, the pharmaceutical company filed an application to consolidate the assessment procedures for pembrolizumab according to Section 35a, paragraph 5b SGB V. At its session on 20 June 2019, the G-BA approved the application for consolidation in accordance with Section 35a, paragraph 5b SGB V.

On 29 November 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient pembrolizumab with the new therapeutic indication

“KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).”

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 March 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of pembrolizumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed 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 arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of pembrolizumab (KEYTRUDA®) in accordance with product information

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Appropriate comparator therapy:

- Bevacizumab in combination with interferon alfa-2a

  or
- Nivolumab in combination with ipilimumab (only for patients with intermediate risk profile)

  or
- Monotherapy with pazopanib

  or
- Monotherapy with sunitinib

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

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Appropriate comparator therapy:

- Nivolumab in combination with ipilimumab

  or
- Sunitinib

  or
- Temsirolimus

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

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

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

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

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

On 1. In terms of authorisation status, the active ingredients aldesleukin, avelumab in combination with axitinib, bevacizumab in combination with interferon alfa-2a, cabozantinib, interferon alfa-2a, ipilimumab in combination with nivolumab, nivolumab in combination with ipilimumab, pazopanib, sunitinib, temsirolimus, and tivozanib are available for the treatment of advanced renal cell carcinoma in previously untreated adults.

On 2. For the patients in this therapeutic indication, it is assumed that surgery and/or radiotherapy with curative objectives are out of the question at the time of the therapy decision and that the treatment is palliative. Non-medicinal treatment is therefore not considered an appropriate comparator therapy. The use of resection and/or radiotherapy as a palliative, patient-individual therapy option for symptom control depending on the localisation and symptomatology of the metastases remains unaffected.

On 3. The following resolutions on the use of medicinal products have been made:

Annex VI of the AM-RL – Prescribability of authorised medicinal products in non-approved therapeutic indications; Part B: Active ingredients that are not prescribable in off-label use (status: June 2019):

- Inhaled interleukin-2 (Proleukin®) for the treatment of renal cell carcinoma – Resolution of 8 June 2016

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

- Ipilimumab in combination with nivolumab: Resolution of 15 August 2019
- Nivolumab in combination with ipilimumab: Resolution of 15 August 2019
- Cabozantinib: Resolution of 6 December 2018
- Tivozanib: Resolution of 19 April 2018

On 4. The general state of medical knowledge on which the findings of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

For the first-line treatment of advanced renal cell carcinoma, the active ingredients avelumab in combination with axitinib, bevacizumab in combination with interferon-alpha, and nivolumab in combination with ipilimumab, pazopanib, sunitinib, or temsirolimus are basically considered as comparator therapies based on the evidence.

Given the evidence provided, bevacizumab in combination with interferon-alpha, pazopanib, sunitinib, and temsirolimus were largely investigated compared with monotherapy with interferon-alpha. It was shown that monotherapy with interferon-alpha has disadvantages with respect to mortality, health-related quality of life, and the frequency of adverse events. Accordingly, after the establishment of the aforementioned therapies, monotherapy with interferon-alpha no longer has any significance for first-line treatment of advanced renal cell carcinoma.

The guidelines distinguish between patients with low/medium and high risk on the basis of risk scores (Motzer/MSKCC[2] score or IMDC[3] score). The IMDC score is consistent with the Motzer/MSKCC score in four of the six risk factors and was developed with tyrosine kinase inhibitor (TKI)-based therapies in mind[4].

Because the therapy options mentioned include TKI, the G-BA considers it appropriate to divide the patient population into two patient groups according to the approved therapeutic indication of pembrolizumab in terms of risk according to the IMDC score (IMDC score 0–2 and IMDC score ≥ 3) and to determine appropriate comparator therapies for both groups.

The pivotal studies on bevacizumab in combination with interferon-alpha, pazopanib, and sunitinib mainly included patients with low or medium risk. Based on the evidence provided, no superior therapeutic benefit can be derived for any of the three therapies mentioned.

For the combination therapy consisting of the checkpoint inhibitors nivolumab and ipilimumab approved since January 2019, the G-BA identified an indication of a considerable additional benefit compared with sunitinib for adult patients with previously untreated advanced renal cell carcinoma and an intermediate risk profile (IMDC score 1–2) in its resolution of 15 August 2019.

Because of the dynamic development of the evidence base with the introduction of several new therapeutic options in this therapeutic indication, the therapeutic standard is currently undergoing change.

Taking this into account, for patients with a favourable or intermediate risk profile (IMDC score 0–2) combination therapy with bevacizumab and interferon-alpha, monotherapy

[2] Memorial Sloan-Kettering Cancer Centre
[3] International Metastatic Renal-Cell Carcinoma Database Consortium
[4] Heng, D.Y., *et al.*, External validation and comparison with other models of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol, 2013. 14(2): p. 141–8.

with pazopanib, and monotherapy with sunitinib, and for patients with intermediate risk profile combination therapy with nivolumab and ipilimumab are currently considered equally appropriate comparator therapies.

For patients with an unfavourable risk profile (IMDC-Score ≥ 3), the current German S3 guideline primarily recommends the use of temsirolimus (with a strong degree of recommendation) but also mentions sunitinib as a treatment option.

The recommendation is based on a Phase III study in which high-risk patients were examined showing an overall survival advantage for temsirolimus compared with interferon-alpha. However, the risk stratification here was based on the five MSKCC criteria and the further defined risk factor “metastases in multiple organs”. However, the comparability of the study population selected based on these criteria with patients assigned to the high risk group according to the IMDC criteria is unclear. The guidelines of “Cancer Care Ontario” (CCO) name sunitinib as an equally adequate treatment option alongside temsirolimus for non-pretreated patients with advanced high-risk renal cell carcinoma.

There is increasing evidence for sunitinib from completed and ongoing randomised clinical trials in which high-risk patients are also treated with sunitinib and in which sunitinib is the comparator therapy. Systematic reviews that allow a comparison between temsirolimus and sunitinib are not available.

For the combination therapy of nivolumab and ipilimumab, the G-BA identified an indication of a considerable additional benefit compared with sunitinib for adult patients with previously untreated advanced renal cell carcinoma and an unfavourable risk profile (IMDC score ≥ 3) in its resolution of 15 August 2019.

Taking into consideration a changing therapeutic standard in this therapeutic indication, the active ingredients temsirolimus and sunitinib as well as the combination therapy of nivolumab and ipilimumab are considered as equally appropriate comparator therapies for patients with an unfavourable risk profile (IMDC score ≥ 3).

In August 2017, the active ingredient tivozanib was approved for first-line treatment of renal cell carcinoma. In the benefit assessment it was established that the additional benefit of tivozanib for patients with a favourable and intermediate prognosis (MSKCC score 0–2) as well as for patients with a poor prognosis (MSKCC score ≥ 3) compared with the appropriate comparator therapy is not proven because no or no suitable data for the assessment of the additional benefit were available (resolution of the G-BA of 19 April 2018). Therefore, tivozanib is not considered an appropriate comparator therapy for both patient groups.

In its resolution of 6 December 2018, the G-BA did not identify any additional benefit for the new therapeutic indication of cabozantinib, which was approved in May 2018 for first-line treatment of advanced renal cell carcinoma in patients at moderate (IMDC score 1–2) or high risk (IMDC score ≥ 3) because the study results on mortality and side effects show neither beneficial nor adverse effects of cabozantinib compared with sunitinib. Therefore, cabozantinib is not considered an appropriate comparator therapy for both patient groups.

Since October 2019, avelumab in combination with axitinib has also been available as first-line treatment for patients with advanced renal cell carcinoma. For avelumab in combination with axitinib, a benefit assessment according to Section 35a SGB V is performed in parallel to this benefit assessment procedure. Avelumab in combination with axitinib is another approved treatment option for patients in this therapeutic indication that is still very new in the first-line treatment of advanced renal cell carcinoma. The therapeutic value can therefore not yet be conclusively assessed. Therefore, avelumab in combination with axitinib is currently not considered an appropriate comparator therapy.

Sunitinib is an appropriate comparator therapy for patients with favourable, intermediate, and poor risk profiles. The combination therapy of nivolumab and ipilimumab is considered an appropriate comparator therapy for patients with an intermediate and unfavourable risk profile. Patients with favourable, intermediate, and poor risk profiles have a different prognosis and therapy response, which is reflected in significant differences in overall survival. In addition, the basic guidelines provide therapy recommendations separately according to risk profile, irrespective of the respective active ingredients. Against the background of a changing therapeutic standard for this therapeutic indication, the G-BA therefore considers it appropriate at the present time to consider the patient populations separately in the benefit assessment despite the overlap of the appropriate comparator therapies for the active ingredients sunitinib as well as nivolumab/ipilimumab depending on the IMDC score (IMDC score 0–2 and IMDC score ≥ 3).

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

Change of the appropriate comparator therapy

For this therapeutic indication, the appropriate comparator therapy was originally determined as follows:

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Appropriate comparator therapy:

- Bevacizumab in combination with interferon alfa-2a

  or
- Monotherapy with pazopanib

  or
- Monotherapy with sunitinib

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Appropriate comparator therapy:

- Sunitinib

  or
- Temsirolimus

With this resolution, the appropriate comparator therapy is supplemented by the combination therapy of the active ingredients nivolumab and ipilimumab according to the approved therapeutic indication in patient group a) and patient group b).

The basis for this change of the appropriate comparator therapy is the resolution of 15 August 2019 on the combination therapy of nivolumab and ipilimumab in this therapeutic indication and corresponding objections in the statements of medical experts in this benefit assessment.

This change in the appropriate comparator therapy neither effects this assessment of additional benefit nor does it require a re-assessment of the benefit assessment.

2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Hint for a considerable additional benefit

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Indication of a considerable additional benefit

Justification:

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

and

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

For the benefit assessment of pembrolizumab in combination with axitinib, the pharmaceutical company presented the randomised, open-label Phase III KEYNOTE 426 study. The ongoing, international, multi-centre study is being conducted in 124 study centres in 16 countries.

Included were adult patients with previously untreated, advanced or metastatic clear cell renal cell carcinoma (Stage IV in accordance with AJCC[5] classification).

In addition to patients with clear cell renal cell carcinoma, patients with a clear cell component were included. Their proportion is 6% of the study population. Patients with non-clear-cell renal cell carcinoma are not included in the study population. The same applies to patients with Karnofsky performance status < 70%. The inclusion of patients was independent of their risk profile; however the IMDC[6] score was collected at the start of study.

861 patients in a 1:1 randomisation were assigned to treatment with pembrolizumab in combination with axitinib (pembrolizumab + axitinib, 432 patients) or the control arm with the appropriate comparator therapy sunitinib (429 patients).

The assignment of patients to the intervention or control arm was stratified by region (North America vs Western Europe vs Rest of the world) and the risk profile in accordance with IMDC score at the start of study (favourable vs intermediate vs unfavourable, defined as presence of 0 vs 1 to 2 vs ≥ 3 risk factors in accordance with IMDC score).

The sub-population of patients with a favourable or intermediate risk profile relevant for this benefit assessment included 376 patients in the pembrolizumab + axitinib arm and 377 patients in the sunitinib arm. The relevant sub-population of patients with an unfavourable risk profile consists of 56 patients in the pembrolizumab + axitinib arm and 52 patients in the sunitinib arm. The mean age of the study participants was 61 years in both the pembrolizumab + axitinib arm and the sunitinib arm.

Treatment was continued until disease progression, the occurrence of unacceptable toxicity, or discontinuation of therapy at the discretion of the doctor/patient. Pembrolizumab was to be administered for a maximum of 35 cycles. However, patients were able to resume treatment with pembrolizumab for another year (second course phase). The prerequisite for this was a

[5] American Joint Committee on Cancer
[6] International Metastatic Renal-Cell Carcinoma Database Consortium

complete, confirmed response or the achievement of the maximum treatment duration with stable disease after subsequent confirmed progression.

Pembrolizumab was given once at the beginning of each 3-week cycle, and axitinib was given continuously. Sunitinib was administered continuously for 4 weeks of a 6-week cycle followed by a 2-week treatment break. Switching between treatment arms (cross-over) was not allowed during the course of the study.

Following study treatment, 22% of patients of the pembrolizumab + axitinib arm with a favourable or intermediate risk profile received systemic antineoplastic follow-up therapy. In the sunitinib arm, this was 37% of patients; nivolumab (16%), sunitinib (6%), and pazopanib (5%) were the most commonly used follow-up therapies for patients in this treatment arm. Of the patients with an unfavourable risk profile, 34% in the pembrolizumab + axitinib arm received systemic antineoplastic follow-up therapy. In the sunitinib arm, this was 44% of patients; nivolumab (29%) as well as sunitinib and pazopanib (each 6%) were especially used follow-up therapies for patients in this treatment arm.

For the ongoing KEYNOTE 426 study, results for the data cut-offs of 24 August 2018 and 2 January 2019 are available. Because of the longer observation period, the results of the 2nd data cut-off of 2 January 2019 are used for this benefit assessment. This is a post-hoc data cut-off of the KEYNOTE 426 study as requested by the European Medicines Agency (EMA).

The study assesses overall survival and endpoints of the morbidity (symptomatology, health status), health-related quality of life, and adverse events categories.

Extent and probability of the additional benefit

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

Mortality

Overall survival

For the endpoint overall survival, there is a statistically significant difference between treatment arms in favour of pembrolizumab + axitinib (hazard ratio (HR): 0.57 95% confidence interval (CI) [0.41; 0.80]; p value: 0.001).

By the time of the underlying data cut-off, 58 patients (15.4%) in the pembrolizumab + axitinib arm and 90 patients (23.9%) in the sunitinib arm had died; the median survival time had not yet been reached in either treatment arm.

The extent of the effect of the combination therapy of pembrolizumab + axitinib compared with sunitinib is considered a significant improvement in overall survival.

Morbidity

Progression-free survival (PFS)

The PFS endpoint is defined as the period from randomisation to the first documentation of disease progression or death by any cause, whichever occurs first. Proof of disease progression is based on RECIST[7] criteria (Version 1.1).

There is a statistically significant difference between the study arms to the benefit of pembrolizumab + axitinib (HR: 0.70 95% CI [0.57; 0.86]; p value: < 0.001). Disease progression occurred in 169 patients (44.9%) in the pembrolizumab + axitinib arm and in 193 patients (51.2%) in the sunitinib arm. The median time to the event is 18.0 months in the intervention arm and 12.5 months in the control arm. This results in an absolute difference of 5.5 months.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the KEYNOTE 426 study, the mortality endpoint component was calculated as an independent endpoint via the overall survival endpoint. The morbidity component was not surveyed on the basis of symptoms but rather exclusively by means of imaging procedures (according to RECIST Version 1.1). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (EORTC QLQ-C30, FKSI-DRS)

The disease symptomatology of the study participants was assessed using the symptom scales of the cancer-specific EORTC QLQ-C30 questionnaire as well as the FKSI-DRS (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms) questionnaire. The FKSI-DRS is a sub-scale of the measuring instrument FKSI-15 and includes 9 questions on specific symptoms in patients with advanced renal carcinoma.

For both questionnaires, the time of data collection differed between the study arms in the first 24 weeks of the study. This means that the burden of treatment during the course of the cycle is not represented equally in the study arms.

In the pembrolizumab + axitinib arm, symptomatology was assessed on day 1 of each 3-week cycle. Pembrolizumab was given once at the beginning of each cycle, and axitinib was given continuously.

[7] Response Evaluation Criteria in Solid Tumours

In contrast, in the sunitinib arm, symptomatology was assessed on day 1 and after 4 weeks on day 29 of a 6-week cycle. Sunitinib was administered continuously for 4 weeks per cycle followed by a 2-week treatment break.

While both treatment arms had potentially lower treatment-related symptoms at the beginning of each cycle, day 29 of each sunitinib cycle (also included in the sunitinib arm evaluation) was a time of potentially high treatment-related stress.

For the control arm, in addition to surveys of time points with potentially lower treatment-related burden, time points with potentially high burden of sunitinib treatment were also considered in the evaluation. There is thus a potential advantage in favour of intervention.

In this benefit assessment procedure, the pharmaceutical company did not submit any further evaluations of the patient-reported endpoints that more appropriately take into account the restrictions resulting from the different data collection times in the study arms.

Overall, the evaluations of the symptomatology are not considered useful because of the possible bias in favour of the intervention.

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

The uncertainties mentioned with regard to the survey of the disease symptoms as a result of different survey times between the study arms also apply to the survey of health-related quality of life using the EQ-5D VAS.

According to the explanations in the “Symptomatology” section, the evaluations on health-related quality of life are therefore also not considered usable.

Quality of life

The health-related quality of life was assessed using the functional scales and the global health status scale of the cancer-specific EORTC QLQ-C30 questionnaire.

The uncertainties mentioned with regard to the survey of the disease symptoms as a result of different survey times between the study arms also apply to the survey of health-related quality of life using the EORTC QLQ-C30 questionnaire.

According to the explanations in the “Symptomatology” section, the evaluations on health-related quality of life are therefore also not considered usable.

Side effects

Adverse events (AE) in total

Almost all study participants experienced AE. The results are only presented as a supplement.

Serious adverse events (SAE)

There is a statistically significant difference to the disadvantage of pembrolizumab + axitinib compared with sunitinib. SAE appear 5.0 months (median) earlier in the pembrolizumab + axitinib arm (19.2 months) than in the sunitinib arm (24.2 months).

In the KEYNOTE 426 study, the survey of SAE was planned for 90 days after the end of treatment or 30 days if a new antineoplastic therapy was started. The observation period is therefore determined by the reasons for therapy discontinuation and here mainly by the disease progression. Disease progression occurred earlier in the control arm. This shortens the median observation time in the control arm compared with the intervention arm.

Severe AE (CTCAE grade ≥ 3)

For the endpoint severe AE (CTCAE grade ≥ 3), there is no statistically significant difference between the treatment arms.

Therapy discontinuations because of AE

With respect the occurrence of therapy discontinuations because of AE, there is a statistically significant difference between the study arms to the disadvantage of pembrolizumab + axitinib. This is based on 127 events (34.0%) in the pembrolizumab + axitinib arm and 53 events (14.2%) in the sunitinib arm.

Specific AE

Immune-mediated AE

With respect to the endpoints immune mediated SAE and immune-mediated severe AE (CTCAE grade ≥ 3), there is a statistically significant difference between the study arms to the detriment of pembrolizumab + axitinib.

Other specific AE

For other specific AEs, both advantages and disadvantages of pembrolizumab + axitinib compared with sunitinib can be identified.

In detail, there are advantages in the endpoints “Blood and lymphatic system disorders” and “Infections and infestations” (in each case: SOC, severe AE [CTCAE grade ≥ 3]).

Pembrolizumab + axitinib has disadvantages compared with sunitinib for the endpoints “Respiratory, thoracic, and mediastinal disorders” and “Endocrine disorders” (SOC, SAE) as well as “Hepatobiliary disorders” and “Renal and urinary disorders” (in each case: SOC, severe AE [CTCAE grade ≥ 3]).

Overall, the results on side effects for pembrolizumab + axitinib compared with sunitinib show disadvantages in SAE and therapy discontinuation because of adverse events. With regard to specific adverse events, both advantages and disadvantages of the combination therapy compared with sunitinib are shown in detail.

<u>Overall assessment</u>

To assess the additional benefit of pembrolizumab in combination with axitinib for the first-line treatment of advanced renal cell carcinoma in adults with a favourable or intermediate risk profile (IMDC score 0–2), results from the KEYNOTE 426 study for the endpoint categories mortality, morbidity, quality of life, and side effects are available.

In the ongoing KEYNOTE 426 study, pembrolizumab in combination with axitinib is compared with the appropriate comparator therapy sunitinib.

The combination therapy of pembrolizumab and axitinib leads to a statistically significant advantage in overall survival over sunitinib.

For the endpoint categories morbidity and health-related quality of life based on the evaluations for the measuring instruments EORTC QLQ-C30, FKSI-DRS, and EQ-5D VAS submitted by the pharmaceutical company, there are no usable data. This is due to different survey times in the study arms, which means that the burden of treatment during the course of the cycle is not represented equally in the study arms. No further evaluations were submitted by the pharmaceutical company in this benefit assessment in order to address the limitations of the data basis and to enable an evaluation. An assessment of how the combination therapy affects the disease-specific symptomatology, health status, and health-related quality of life of patients is therefore not possible on the basis of the data submitted by the pharmaceutical company for the benefit assessment.

In the endpoint category side effects, the combination therapy shows disadvantages for serious adverse events and therapy discontinuation because of adverse events compared with sunitinib. For the specific adverse events, both advantages and disadvantages can be identified in detail.

In the overall assessment of the results on the patient-relevant endpoints, the G-BA concludes that the clear advantage in overall survival outweighs the disadvantages in terms of serious side effects and therapy discontinuation. There is a significant improvement in the therapy-relevant benefit that has not yet been achieved.

As a result, the G-BA found a considerable additional benefit for pembrolizumab in combination with axitinib for the first-line treatment of advanced renal cell carcinoma in adults with a favourable or intermediate risk profile (IMDC score ≥ 0–2) compared with the appropriate comparator therapy sunitinib.

Reliability of data (probability of additional benefit)

The randomised, open-label Phase III KEYNOTE 426 study compared pembrolizumab in combination with axitinib with the appropriate comparator therapy sunitinib. The risk of bias at the study level is classified as low.

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

With respect to the overall survival endpoint, there are uncertainties because of the still preliminary results based on relatively low event numbers. Thus, by the time of the underlying data cut-off, 15.4% of the patients in the pembrolizumab + axitinib arm and 23.9% in the sunitinib arm had died; the median survival time had not yet been reached in either case.

Furthermore, there are no usable data for the morbidity and health-related quality of life endpoint categories. This is due to the different survey times for the patient-reported endpoints in the study arms, which means that the burden of treatment over the course of the cycle is not represented equally in the study arms. As a result, for the control arm, in addition to surveys of time points with potentially lower treatment-related burden, time points with potentially high burden of sunitinib treatment are also considered in the evaluation. There is thus a potential advantage in favour of intervention. Therefore, no statements can be made on the effect of pembrolizumab in combination with axitinib on the morbidity and health-related quality of life of patients.

Overall, the present data basis is subject to uncertainties. In conclusion, these limit the reliability of the information provided. As a result, the reliability of the additional benefit identified is classified in the “hint” category.

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

Mortality

Overall survival

There is a statistically significant difference between the treatment arms to the benefit of pembrolizumab + axitinib (HR: 0.50 95% CI [0.29; 0.87]; p value: 0.015). The median survival time is 21.8 months in the intervention arm and 10.1 months in the control arm; this corresponds to an absolute difference of 11.7 months.

The extent of the effect of the combination therapy of pembrolizumab + axitinib compared with sunitinib is considered a significant improvement in overall survival.

Morbidity

Progression-free survival (PFS)

The PFS endpoint is defined as the period from randomisation to the first documentation of disease progression or death by any cause, whichever occurs first. Proof of disease progression is based on RECIST criteria (Version 1.1).

There is a statistically significant difference between the study arms to the benefit of pembrolizumab + axitinib (HR: 0.57 95% CI [0.35; 0.92]; p value: 0.002). Disease progression occurred in 38 patients (67.9%) in the pembrolizumab + axitinib arm and in 39 patients (75.0%) in the sunitinib arm. The median time to the event is 4.9 months in the intervention arm and 2.9 months in the control arm. This results in an absolute difference of 3.0 months.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the KEYNOTE 426 study, the mortality endpoint component was calculated as an independent endpoint via the overall survival endpoint. The morbidity component was not surveyed on the basis of symptoms but rather exclusively by means of imaging procedures (according to RECIST Version 1.1). Taking the aforementioned factors into consideration, there are differing opinions within the G-BA regarding the relevance for patients of the PFS endpoint. The overall statement on the extent of the additional benefit remains unaffected.

Symptomatology (EORTC QLQ-C30, FKSI-DRS)

The disease symptomatology of the study participants was assessed using the symptom scales of the cancer-specific EORTC QLQ-C30 questionnaire as well as the FKSI-DRS (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms) questionnaire. The FKSI-DRS is a sub-scale of the measuring instrument FKSI-15 and includes 9 questions on specific symptoms in patients with advanced renal carcinoma.

For both questionnaires, the time of data collection differed between the study arms in the first 24 weeks of the study. This means that the burden of treatment during the course of the cycle is not represented equally in the study arms.

In the pembrolizumab + axitinib arm, symptomatology was assessed on day 1 of each 3-week cycle. Pembrolizumab was given once at the beginning of each cycle, and axitinib was given continuously.

In contrast, in the sunitinib arm, symptomatology was assessed on day 1 and after 4 weeks on day 29 of a 6-week cycle. Sunitinib was administered continuously for 4 weeks per cycle followed by a 2-week treatment break.

While both treatment arms had potentially lower treatment-related symptoms at the beginning of each cycle, day 29 of each sunitinib cycle (also included in the sunitinib arm evaluation) was a time of potentially high treatment-related stress.

For the control arm, in addition to surveys of time points with potentially lower treatment-related burden, time points with potentially high burden of sunitinib treatment were also considered in the evaluation, thus potentially giving an advantage in favour of intervention.

In this benefit assessment procedure, the pharmaceutical company did not submit any further evaluations of the patient-reported endpoints that more appropriately take into account the restrictions resulting from the different data collection times in the study arms.

Overall, the evaluations of the symptomatology are not considered useful because of the possible bias in favour of the intervention.

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire.

The uncertainties mentioned with regard to the survey of the disease symptoms as a result of different survey times between the study arms similarly apply to the survey of health-related quality of life using the EQ-5D VAS.

Thus, in accordance with the explanations in the "Symptomatology" section, the evaluations on the state of health are also not considered usable.

Quality of life

The health-related quality of life was assessed using the functional scales and the global health status scale of the cancer-specific EORTC QLQ-C30 questionnaire.

The uncertainties mentioned in connection with the survey of the disease symptoms as a result of different survey times between the study arms also apply to the survey of health-related quality of life using the EORTC QLQ-C30 questionnaire.

According to the explanations in the "Symptomatology" section, the evaluations on health-related quality of life are therefore also not considered usable.

Side effects

Adverse events (AE) in total

Almost all study participants experienced AE. The results are only presented as a supplement.

Serious adverse events (SAE), therapy discontinuation because of AE

There are no statistically significant differences between the treatment arms in terms of both SAE and therapy discontinuations because of AE.

In the KEYNOTE 426 study, the planned follow-up time for SAE was 90 days or 30 days if a new antineoplastic therapy was started. The observation period is therefore determined by the reasons for therapy discontinuation and here mainly by the disease progression. Disease progression occurred earlier in the control arm. This shortens the median observation time in the control arm compared with the intervention arm.

Severe AE (CTCAE grade ≥ 3)

For the endpoint severe AE (CTCAE grade ≥ 3), there is a statistically significant difference between treatment arms in favour of pembrolizumab + axitinib. Severe AE (CTCAE grade ≥ 3) appear 1.7 months (median) later in the pembrolizumab + axitinib arm (2.7 months) than in the sunitinib arm (1.0 months).

Specific AE

Immune-mediated AE

For the endpoints immune-mediated SAE and immune-mediated severe AE (CTCAE grade ≥ 3), there is no statistically significant difference between the treatment arms.

Other specific AE

For other specific AE, there are only advantages for treatment with pembrolizumab + axitinib compared with sunitinib. In detail, there are positive effects in the endpoints "Nervous system disorders (SOC, AE), "Blood and lymphatic system disorders, "General disorders and

administration site conditions", and "Metabolism and nutrition disorders" (in each case: SOC, severe AE [CTCAE grade ≥ 3]).

Overall, the results on side effects for pembrolizumab + axitinib compared with sunitinib show an advantage in severe adverse events (CTCAE grade ≥ 3). Also in terms of specific adverse events, the combination therapy has only advantages over sunitinib.

Overall assessment

To assess the additional benefit of pembrolizumab in combination with axitinib for the first-line treatment of advanced renal cell carcinoma in adults with an unfavourable risk profile (IMDC score ≥ 3), results from the KEYNOTE 426 study for the endpoint categories mortality, morbidity, quality of life, and side effects are available.

In the ongoing KEYNOTE 426 study, pembrolizumab in combination with axitinib is compared with the appropriate comparator therapy sunitinib.

The combination therapy of pembrolizumab and axitinib leads to a statistically significant advantage in overall survival over sunitinib.

For the endpoint categories morbidity and health-related quality of life based on the evaluations for the measuring instruments EORTC QLQ-C30, FKSI-DRS, and EQ-5D VAS submitted by the pharmaceutical company, there are no usable data. This is due to different survey times in the study arms, which means that the burden of treatment during the course of the cycle is not represented equally in the study arms. No further evaluations were submitted by the pharmaceutical company in this benefit assessment in order to address the limitations of the data basis and to enable an evaluation.

An assessment of how the combination therapy affects the disease-specific symptomatology, health status, and health-related quality of life of patients is therefore not possible on the basis of the data submitted by the pharmaceutical company for the benefit assessment.

In the endpoint category side effects, the combination therapy shows an advantage compared with sunitinib in severe adverse events (CTCAE grade ≥ 3). For specific adverse events, only advantages of pembrolizumab in combination with axitinib compared with sunitinib can be found in detail.

In the overall assessment of the results on the patient-relevant endpoints, the advantages in overall survival and the reduction of severe side effects are assessed overall as a significant improvement in the therapy-relevant benefit.

As a result, the G-BA found a considerable additional benefit for pembrolizumab in combination with axitinib for the first-line treatment of advanced renal cell carcinoma in adults with an unfavourable risk profile (IMDC score ≥ 3) compared with the appropriate comparator therapy sunitinib.

Reliability of data (probability of additional benefit)

The randomised, open-label Phase III KEYNOTE 426 study compared pembrolizumab in combination with axitinib with the appropriate comparator therapy sunitinib. The risk of bias at the study level is classified as low.

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

There are no usable data for the morbidity and health-related quality of life endpoint categories. This is due to the different survey times for the patient-reported endpoints in the study arms, which means that the burden of treatment over the course of the cycle is not represented equally in the study arms. As a result, for the control arm, in addition to surveys of time points with potentially lower treatment-related burden, time points with potentially high burden of sunitinib treatment are also considered in the evaluation. There is thus a potential advantage

in favour of intervention. Therefore, no statements can be made on the effect of pembrolizumab in combination with axitinib on the morbidity and health-related quality of life of patients.

Overall, the present data basis is subject to uncertainties. The uncertainties are not considered to be so high overall that a downgrading of the reliability of data would be justified for the overall assessment. In particular, the risk of bias of the endpoint overall survival is considered low. The reliability of data supporting the finding of an additional benefit must therefore be classified as “indication”.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient pembrolizumab in combination with axitinib.

The therapeutic indication assessed here is as follows:

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)

and

b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)

About patient group a)

The appropriate comparator therapy was determined by the G-BA as follows:

- Bevacizumab in combination with interferon alfa-2a

  or
- Nivolumab in combination with ipilimumab (only for patients with intermediate risk profile)

  or
- Monotherapy with pazopanib

  or
- Monotherapy with sunitinib

For the benefit assessment, the pharmaceutical company presented the randomised, open-label, multi-centre Phase III KEYNOTE 426 study.

In the ongoing study, pembrolizumab in combination with axitinib is compared with the appropriate comparator therapy sunitinib.

The combination therapy of pembrolizumab and axitinib leads to a clear advantage in overall survival over sunitinib.

No usable data are available for morbidity and health-related quality of life. The reason for this is the different survey times in the study arms, which means that the burden of treatment during the course of the cycle is not represented equally in the study arms. It is therefore not possible to assess how the combination therapy affects, for example, the disease-specific symptomatology and the health-related quality of life of the patients.

For side effects, pembrolizumab in combination with axitinib has disadvantages compared with sunitinib in terms of serious adverse events and therapy discontinuation because of adverse events. For the specific adverse events, both advantages and disadvantages can be observed.

There are uncertainties because of the still relatively low number of events for the overall survival endpoint and the lack of usable data on the endpoint categories morbidity and health-related quality of life.

Overall, the G-BA comes to the conclusion that the advantage in overall survival outweighs the disadvantages in terms of side effects.

In the overall view, there is a hint for a considerable additional benefit of pembrolizumab in combination with axitinib compared with sunitinib.

About patient group b)

The appropriate comparator therapy was determined by the G-BA as follows:

- Nivolumab in combination with ipilimumab

  or
- Sunitinib

  or
- Temsirolimus

For the benefit assessment, the pharmaceutical company presented the randomised, open-label, multi-centre Phase III KEYNOTE 426 study in which pembrolizumab in combination with axitinib was compared with the appropriate comparator therapy sunitinib.

The combination therapy of pembrolizumab and axitinib leads to a clear advantage in overall survival over sunitinib.

No usable data are available for morbidity and health-related quality of life. The reason for this is the different survey times in the study arms, which means that the burden of treatment during the course of the cycle is not represented equally in the study arms. It is therefore not possible to assess how the combination therapy affects, for example, the disease-specific symptomatology and the health-related quality of life of the patients.

For side effects, pembrolizumab in combination with axitinib has an advantage compared with sunitinib in terms of severe adverse events (CTCAE grade ≥ 3). For the specific adverse events, only pembrolizumab in combination with axitinib has advantages compared with sunitinib.

Overall, the advantages in overall survival and severe side effects represent a significant improvement in therapy-relevant benefits.

In the overall view, there is an indication of a considerable additional benefit of pembrolizumab in combination with axitinib compared with sunitinib.

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 patient figures presented by the pharmaceutical company for a) patients with a favourable or intermediate risk profile (IMDC score 0–2) (approx. 3,050–3,310 patients) and b) patients with an unfavourable risk profile (IMDC score ≥ 3): (approx. 460–610 patients) are subject to uncertainties and assessed as slightly overestimated overall. This is due to the higher incidences extrapolated by the pharmaceutical company for 2018 (upper limit) and 2019 for the calculation of the number of patients with renal cell carcinoma compared with the current incidence forecast of the Robert Koch Institute for 2020. For both questions the proportions of patients are also subject to uncertainty with regard to the risk profiles.

Against the background of the uncertainties mentioned, the resolution is based on the number of patients with advanced renal cell carcinoma (RCC) eligible for first-line treatment according to the information provided by the IQWiG. These are based on the calculations of patient numbers in the Addendum to Order A19-95 (G20-06) within the framework of the benefit assessment procedure according to Section 35a SGB V for the active ingredient avelumab (resolution of 14 May 2020). Although these figures are also subject to uncertainties (see below), they are assessed as a more precise estimate of the number of patients in the SHI target population.

The target population is calculated via five calculation steps:

1. The predicted incidence for patients with renal carcinoma is approx. 15,400 for 2020.
2. Of these, 14,784 patients (96%) have renal cell carcinoma (RCC).
3. 2,085 patients (14.1%) have advanced RCC with an initial diagnosis in UICC stage IV+. For patients with an initial diagnosis in UICC stage I–III (85.9%), 1,930 (15.2%) progress to stage IV. This results in a total of 4,015 patients with advanced RCC.
4. There are 3,071 patients (76.5%) with a favourable and intermediate risk profile (IMDC 0–2). 943 patients (23.4%) have an unfavourable risk profile (IMDC ≥ 3).
5. Applying a SHI-insured proportion of 88.0%, approx. 2,700 patients in the SHI target population have a favourable or intermediate risk profile (IMDC score 0–2). Approx. 830 patients in the SHI target population have an unfavourable risk profile (IMDC-Score ≥ 3).

With the breakdown by risk profile, there are uncertainties mainly because of a relatively high rate of missing values in the publication by Goebell et al.

It should also be considered that stage IV of UICC classification also includes patients with locally advanced disease without remote metastases or without evidence of regional lymph node metastases. It is unclear whether this patient group is eligible for systemic therapy or initially for surgical therapy.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for KEYTRUDA® (active ingredient: pembrolizumab) at the following publicly accessible link (last access: 5 May 2020):

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

Treatment with pembrolizumab in combination with axitinib may only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in internal medicine and nephrology, and other specialists participating in the Oncology Agreement who are experienced in the treatment of patients with renal cell carcinoma.

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

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

The KEYNOTE 426 study exclusively investigated patients with renal cell carcinoma with clear cell histology. No data are available for patients with non-clear-cell renal cell carcinoma.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2020).

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

Treatment duration:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", time between individual treatments, and for maximum treatment duration if specified in the product information.

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 in combination with axitinib				
Pembrolizumab	1 × per 21-day cycle	17.4	1	17.4
Axitinib	2 × daily	365	1	365
Appropriate comparator therapy				
a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)				
Bevacizumab in combination with interferon alfa-2a				
Bevacizumab	1 × every 14 days	26.1	1	26.1
Interferon alfa-2a	3 × within 7 days	156.4	1	156.4
Nivolumab in combination with ipilimumab				
Initial treatment				
Nivolumab	1 × per 21-day cycle	4	1	4
Ipilimumab				
Follow-up treatment				
Nivolumab	1 x per 14-day cycle (3 weeks after last dose of initial treatment)	20.1	1	20.1
	or			

(Continuation)

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
	1 x per 28-day cycle (6 weeks after last dose of initial treatment)	9.3	1	9.3
Monotherapies				
Pazopanib	1 × daily	365	1	365
Sunitinib	1 × daily for 28 days followed by a 14-day treatment break.	8.7 cycles	28	243.6
b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)				
Nivolumab in combination with ipilimumab				
Initial treatment				
Nivolumab	1 × per 21-day cycle	4	1	4
Ipilimumab				
Follow-up treatment				
Nivolumab	1 x per 14-day cycle (3 weeks after last dose of initial treatment)	20.1	1	20.1
	or			
	1 x per 28-day cycle (6 weeks after last dose of initial treatment)	9.3	1	9.3
Monotherapies				
Sunitinib	1 × daily for 28 days followed by a 14-day treatment break.	8.7 cycles	28	243.6
Temsirolimus	1 × every 7 days	52.1	1	52.1

Usage and consumption:

For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were used as a basis (average body weight: 77.0 kg)[8].

[8] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Pembrolizumab in combination with axitinib					
Pembrolizumab	200 mg	200 mg	2 × 100 mg	17.4	34.8 × 100 mg
Axitinib	5 mg	10 mg	2 × 5 mg	365	730 × 5 mg
Appropriate comparator therapy					
a) Adult patients with untreated advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2)					
Bevacizumab in combination with interferon alfa-2a					
Bevacizumab	10 mg/kg BW	770 mg	2 × 400 mg	26.1	52.2 × 400 mg
Interferon alfa-2a	9 million I.U.	9 million I.U.	1 × 9 million I.U.	156.4	156.4 × 9 million I.U.
Nivolumab in combination with ipilimumab					
Initial treatment					
Nivolumab	3 mg/kg BW	231 mg	2 × 100 mg 1 × 40 m	4	8 × 100 mg 4 × 40 mg
Ipilimumab	1 mg/kg BW	77 mg	2 × 50 mg	4	8 × 50 mg
Follow-up treatment					
Nivolumab	240 mg	240 mg	2 × 100 mg 1 × 40 mg	20.1	40.2 × 100 mg 20.1 × 40 mg
	or				
	480 mg	480 mg	4 × 100 mg 2 × 40 mg	9.3	37.2 × 100 mg 18.6 × 40 mg
Monotherapies					
Pazopanib	800 mg	800 mg	2 × 400 mg	365	730 × 400 mg
Sunitinib	50 mg	50 mg	1 × 50 mg	243.6	243.6 × 50 mg
b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)					
Nivolumab in combination with ipilimumab					
Initial treatment					
Nivolumab	3 mg/kg BW	231 mg	2 × 100 mg 1 × 40 m	4	8 × 100 mg 4 × 40 mg

(Continuation)

Ipilimumab	1 mg/kg BW	77 mg	2 × 50 mg	4	8 × 50 mg
Follow-up treatment					
Nivolumab	240 mg	240 mg	2 × 100 mg 1 × 40 mg	20.1	40.2 × 100 mg 20.1 × 40 mg
	or				
	480 mg	480 mg	4 × 100 mg 2 × 40 mg	9.3	37.2 × 100 mg 18.6 × 40 mg
Monotherapies					
Sunitinib	50 mg	50 mg	1 × 50 mg	243.6	243.6 × 50 mg
Temsirolimus	25 mg	25 mg	1 × 30 mg	52.1	52.1 × 30 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 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 product:

Designation of the therapy	Package 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	€ 3,083.93	€ 1.77	€ 172.85	€ 2,909.31
Axitinib	56 FCT	€ 3,597.14	€ 1.77	€ 0.00	€ 3,595.37
Appropriate comparator therapy					
Bevacizumab	1 CIS	€ 1,689.86	€ 1.77	€ 93.23	€ 1,594.86
Interferon alfa-2a	30 PFS	€ 3,153.39	€ 1.77	€ 176.81	€ 2,974.81
Ipilimumab	1 vial, 50 mg	€ 3,849.07	€ 1.77	€ 216.54	€ 3,630.76
Nivolumab	1 vial, 40 mg	€ 544.32	€ 1.77	€ 29.53	€ 513.02
Nivolumab	1 vial, 100 mg	€ 1,344.24	€ 1.77	€ 73.81	€ 1,268.66
Pazopanib	60 FCT	€ 4,740.73	€ 1.77	€ 267.47	€ 4,471.49
Sunitinib	30 HC	€ 7,214.07	€ 1.77	€ 408.72	€ 6,803.58
Temsirolimus	1 CIS	€ 1,182.86	€ 1.77	€ 64.88	€ 1,116.21
Abbreviations: PFS = prefilled syringes, FCT = film-coated tablets, HC = hard capsules, CIS = concentrate for the preparation of an infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 April 2020

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 assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

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

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

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 12 June 2018.

The appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 10 December 2018.

On 29 November 2019, the pharmaceutical company submitted a dossier for the benefit assessment of pembrolizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 2.

By letter dated 29 November 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient pembrolizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 March 2020. The deadline for submitting written statements was 23 March 2020.

The oral hearing was held on 6 April 2020.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 5 May 2020, and the proposed resolution was approved.

At its session on 14 May 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	12 June 2018	Determination of the appropriate comparator therapy
Subcommittee Medicinal Products	10 December 2018	Redefinition of the appropriate comparator therapy
Working group Section 35a	1 April 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	6 April 2020	Conduct of the oral hearing
Working group Section 35a	14 April 2020 29 April 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	5 May 2020	Concluding discussion of the draft resolution
Plenum	14 May 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 14 May 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken