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 Avelumab (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 avelumab (Bavencio®) was listed for the first time on 15 October 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 24 October 2019, avelumab 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) No. 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 20 November 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient avelumab with the new therapeutic indication in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication)

“Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) (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 avelumab 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, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 avelumab.

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 avelumab (Bavencio ®) in accordance with product information

Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) (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, bevacizumab in combination with interferon alfa-2a, cabozantinib, interferon alfa-2a, ipilimumab in combination with nivolumab, nivolumab in combination with ipilimumab, pazopanib, pembrolizumab in combination with axitinib, 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 bevacizumab in combination with interferon-alpha, nivolumab in combination with ipilimumab, pazopanib, and pembrolizumab in combination with axitinib, 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 avelumab 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 August 2019, pembrolizumab in combination with axitinib has also been available as first-line treatment for patients with advanced renal cell carcinoma. For pembrolizumab in combination with axitinib, a benefit assessment according to Section 35a SGB V is performed in parallel to this benefit assessment procedure. Pembrolizumab 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, pembrolizumab 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 avelumab is assessed as follows.

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

An additional benefit is not proven

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

Hint for 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 avelumab in combination with axitinib, the pharmaceutical company presented the randomised, open-label Phase III Javelin Renal 101 study. The ongoing, international, multi-centre study is being conducted in 156 study centres in 21 countries.

The study included adult patients with histologically or cytologically confirmed, previously untreated, advanced, or metastasised clear cell renal cell carcinoma.

In addition to patients with clear cell renal cell carcinoma, patients with a clear cell component were included. Their proportion is less than 0.2% 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[5] score was collected at the start of study.

In a 1:1 randomisation, 886 patients were assigned to treatment with avelumab in combination with axitinib (avelumab + axitinib, 442 patients) or the control arm with the appropriate comparator therapy sunitinib (446 patients).

The assignment of patients to the intervention or control arm was stratified by region (US vs Canada/Western Europe vs Rest of the World) and ECOG performance status (0 vs 1).

The sub-population of patients with a favourable or intermediate risk profile relevant for this benefit assessment included 365 patients in the avelumab + axitinib arm and 372 patients in the sunitinib arm. The relevant sub-population of patients with an unfavourable risk profile consists of 72 patients in the avelumab + axitinib arm and 71 patients in the sunitinib arm. For 6 of the patients included in the study, no information on the IMDC score was available. They could therefore not be assigned to either sub-population. The mean age of the study participants was 61 years in both the avelumab + axitinib arm and the sunitinib arm.

Treatment was continued until disease progression, the occurrence of unacceptable toxicity, the discontinuation of therapy at the patient's discretion, and the end of the study, among other things. At the investigator's discretion, the patients were able to remain on treatment with the study medication beyond disease progression as long as they continued to benefit from the treatment.

[5] International Metastatic Renal-Cell Carcinoma Database Consortium

Avelumab was given once at the beginning of each 2-week cycle, and axitinib was given continuously. Avelumab was administered at a dose of 10 mg/kg body weight depending on body weight. According to the product information, avelumab is to be administered in a dosage of 800 mg every 2 weeks regardless of body weight. In the opinion of the EMA, the 2 dosage regimens (not dependent or dependent on body weight) are comparable in terms of efficacy and safety, which is why the weight-independent dosage of avelumab was adopted by the EMA for this new indication and finally approved.

Sunitinib was administered continuously for 4 weeks of a 6-week cycle followed by a 2-week treatment break.

Following study treatment, 31% of patients of the avelumab + axitinib arm with a favourable or intermediate risk profile received systemic antineoplastic follow-up therapy. In the sunitinib arm, this was 52% of patients, whereby nivolumab (35%), cabozantinib (10%), and axitinib (7%) were the most commonly used follow-up therapies for patients in this treatment arm. In the case of patients with an unfavourable risk profile, 33% in the avelumab + axitinib arm received systemic antineoplastic follow-up therapy. In the sunitinib arm, this was 48% of patients, whereby nivolumab (29%), cabozantinib (11%), and sunitinib (7%) were the most commonly used follow-up therapies for patients in this treatment arm.

For the ongoing Javelin Renal 101 study, results for the pre-specified data cut-offs of 20 June 2018 and 28 January 2019 are available. Because of the longer observation period, the results of the 2nd data cut-off of 28 January 2019 are used for this benefit assessment.

Among other things, overall survival, endpoints of the category morbidity (symptomatology, health status), and adverse events are surveyed.

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 was no statistically significant difference between the treatment groups.

By the time of the underlying data cut-off, 74 patients (20.3%) in the avelumab + axitinib arm and 84 patients (22.6%) in the sunitinib arm had died; the median survival time had not yet been reached in either treatment arm.

Morbidity

Progression-free survival (PFS)

The endpoint PFS is defined as the time from randomisation to the first documentation of disease progression or to death by any cause, whichever comes first. Proof of disease progression is based on RECIST[6] criteria (Version 1.1).

There is a statistically significant difference between the study arms to the benefit of avelumab + axitinib (Hazard Ratio (HR): 0.57 95% confidence interval (CI) [0.44; 0.74]; p value: < 0.0001). Disease progression occurred in 97 patients (26.6%) in the avelumab + axitinib arm and in 142 patients (38.2%) in the sunitinib arm. The median time to the event was not yet reached in both treatment arms.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the Javelin Renal 101 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.

For the interpretation of the PFS results, the data available on morbidity and health-related quality of life are used. Data on morbidity and health-related quality of life are potentially relevant in this respect, especially when, as in the present case, a radiologically determined disease progression is associated with effects on morbidity and/or quality of life.

The data from the Javelin Renal 101 study show no differences between treatment groups in the endpoint category morbidity. Prolonged PFS under avelumab in combination with axitinib was thus not associated with a morbidity benefit. For health-related quality of life, there are no usable data for the benefit assessment.

In summary, the data available do not suggest that the statistically significant prolongation of progression-free survival under combination therapy of avelumab and axitinib – radiologically determined disease progression according to the RECIST criteria – is associated with an improvement in morbidity; usable data for health-related quality of life are not available.

The results on the endpoint PFS are not therefore used in this assessment.

Symptomatology (FKSI-DRS)

The disease symptomatology of the study participants was assessed with 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.

[6] Response Evaluation Criteria in Solid Tumours

As a primary analysis, the pharmaceutical company presented an evaluation from a mixed model for repeated measurements (MMRM) for the mean change in disease-related symptoms (FKSI-DRS overall score) over the course of the study. In the evaluations submitted with the dossier, more than 10% of patients were completely absent. Moreover, contrary to the original planning in the Javelin Renal 101 study, only values collected under treatment were included in the MMRM evaluations.

In the written statement, the pharmaceutical company submitted further MMRM evaluations, which include all available survey dates even after therapy discontinuation. Thus, 92% of the randomised patients in each study arm are included in the evaluation.

There was no statistically significant difference between the study arms.

As a further supporting analysis, the dossier included *post hoc* MMRM evaluations of further sub-scales of individual items of the FKSI-19 questionnaire (see also "Health-related quality of life" section). Because the sub-scales have not been validated and some of the individual items are already covered by the FKSI-DRS or do not represent the symptoms, the evaluations described are not considered for this assessment.

In the dossier, the pharmaceutical company also presented additional analyses in the form of evaluations of the time to the 1st deterioration as well as the time to the 1st final deterioration by a Minimal important Difference (MID) of 3 points. Although responder analyses based on an MID for a clinical assessment of effects have general advantages over an analysis of mean differences, the G-BA does not use the additional responder analyses submitted by the pharmaceutical company in this assessment to assess the effects on the symptomatology because the MID is not validated.

Health status (EQ-5D VAS)

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

As a primary analysis, the pharmaceutical company presented a MMRM evaluation for the mean change over the course of the study. As in the "Symptomatology" section, more than 10% of the patients were completely absent from the evaluations submitted with the dossier. Contrary to the original planning in the Javelin Renal 101 study, only values collected under treatment were included in the MMRM evaluations.

In the written statement, the pharmaceutical company submitted further MMRM evaluations, which include all available survey dates even after therapy discontinuation. Thus, 92% of the randomised patients per study arm can be included in the evaluation.

There was no statistically significant difference between the study arms.

Overall, in the endpoint category morbidity, avelumab in combination with axitinib has neither an advantage nor a disadvantage compared with sunitinib.

Quality of life

For the assessment of health-related quality of life, the pharmaceutical company presented evaluations of the FKSI-19 measuring instrument. The FKSI-19 is a version of the disease-specific measuring instrument FKSI-15 extended by four questions. The disease-related symptomatology of patients with advanced renal carcinoma surveyed by the FKSI-15 is measured using the FKSI-DRS sub-scale and included in the endpoint category morbidity.

The 6 further questions of FKSI-15 that go beyond the FKSI-DRS are not suitable for a comprehensive view of the complex construct of health-related quality of life. Furthermore, for the FKSI-19, the criteria for selecting the 4 additional questions are not described, and the reliability of these items was not examined.

Against this background, the evaluations based on the FKSI-19 submitted by the pharmaceutical company are not used to assess the additional benefit in the endpoint category quality of life.

Side effects

In the Javelin Renal 101 study, the planned follow-up period for all endpoints in the side effects category was 90 days after the last dose of study medication or until the start of follow-up therapy for non-serious side effects (whichever occurred first). Contrary to the pre-specified procedure, for the benefit assessment, the pharmaceutical company submitted only evaluations of the side effects that included only events that occurred up to 30 days after the last dose of the study medication or up to the start of a follow-up therapy (if this occurred earlier).

Adverse events (AE) in total

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

Serious adverse events (SAE), severe AE (CTCAE grade ≥ 3)

For the endpoints SAE and severe AE (CTCAE grade ≥ 3), there are no statistically significant differences between the treatment arms.

Therapy discontinuations because of AE

There is a statistically significant difference between the treatment arms to the disadvantage of avelumab + axitinib. This is based on 86 events (24.0%) in the avelumab + axitinib arm and 49 events (13.3%) in the sunitinib arm.

Specific AE

Immune-mediated AE

In the Javelin Renal 101 study, a potential immune-mediated AE was initially identified using an *a priori* defined list of preferred terms. However, from the AE determined this way, only the following were regarded as immune-mediated AE:
- events in which additional treatment (e.g. with corticosteroids or hormone therapy) was administered and no clear alternative explanation for the AE other than immune-mediated aetiology was available
and/or
- events in which a histopathology/biopsy compatible with an immune-mediated mechanism was required.

The operationalisation of the endpoint immune-mediated AE chosen in the study is assessed as not sufficiently reliable because of the causal link to a successful treatment and the lack of a clear alternative aetiology because it does not guarantee that all immune-mediated AE are covered. The data on immune-mediated AE are thus not considered usable.

Other specific AE

For other specific AE, advantages and disadvantages of avelumab + axitinib compared with sunitinib can be identified.

In detail, there are advantages in the endpoints “Blood and lymphatic system disorders” (SOC, severe AE [CTCAE grade ≥ 3]) as well as “dyspepsia” and “taste disorder” (PT, AE).

Compared with sunitinib, the combination therapy has disadvantages for the endpoints “diarrhoea” and “increased alanine aminotransferase” (in each case: PT, severe AE [CTCAE grade ≥ 3]), “chills”, “pruritus”, and “dysfonia” (in each case: PT, AE), and “Injury, poisoning, and procedural complications” (SOC, AE).

For the specific AE “infusion-related reactions”, there are no usable data because in the Javelin Renal 101 study, infusions were administered only in the avelumab + axitinib arm.

Overall, the results on side effects for avelumab + axitinib compared with sunitinib show a disadvantage for the endpoint therapy discontinuation because of adverse events. In specific adverse events, in detail there are advantages and disadvantages of combination therapy compared with sunitinib.

Overall assessment

For the assessment of the additional benefit of avelumab in combination with axitinib for first-line treatment in adult patients with advanced renal cell carcinoma with a favourable or intermediate risk profile (IMDC score 0–2), results for the endpoint categories mortality, morbidity, and side effects based on the Javelin Renal 101 study are available.

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

For the endpoint overall survival, there was no statistically significant difference between the treatment groups. 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, 20% of the patients in the avelumab + axitinib arm and 23% in the sunitinib arm had died; the median survival time had not yet been reached in either case.

In the endpoint category morbidity, evaluations for disease-specific symptoms using the measuring instrument FKSI-DRS and for health status using the EQ-5D VAS are available. In terms of both disease-related symptomatology of the patients and their health status, neither advantages nor disadvantages of the combination therapy compared with sunitinib can be identified.

Health-related quality of life data have not been submitted. An assessment of the influence of avelumab in combination with axitinib on the quality of life of patients is therefore not possible.

For side effects, avelumab in combination with axitinib has a moderate disadvantage compared with sunitinib in terms of therapy discontinuation because of adverse events. In specific adverse events, in detail there are advantages and disadvantages of combination therapy compared with sunitinib. Because the pharmaceutical company deviated from the a priori planned procedure in the Javelin Real 101 studies for the evaluations of adverse events for the benefit assessment, uncertainties remain with regard to the results in the endpoint category side effects.

In the overall assessment of the results for the patient-relevant endpoints, avelumab in combination with axitinib has a moderate disadvantage in terms of side effects for therapy discontinuation because of adverse events. However, the disadvantage does not reach a level that would justify a lower benefit.

As a result, the G-BA concluded that avelumab in combination with axitinib for the first-line treatment of adults with advanced renal cell carcinoma with a favourable or intermediate risk

profile (IMDC score 0–2) has no proven additional benefit compared with the appropriate comparator therapy sunitinib.

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 avelumab + axitinib (HR: 0.50 95% CI [0.31; 0.81]; p value: 0.005). The median survival time is 21.2 months in the intervention arm and 11.0 months in the control arm; this corresponds to an absolute difference of 10.2 months.

There is also an effect modification for the endpoint overall survival by the characteristic "region". For the sub-groups "North America", "Europe", and "Asia", no statistically significant differences between the treatment arms can be identified. In contrast, for the sub-group "Rest of the World", there is a statistically significant difference between treatment arms in favour of avelumab + axitinib (HR: 0.15 95% CI [0.04; 0.65]; p value: 0.005). The median survival time in the sub-group "Rest of the World" is 19.9 months in the avelumab + axitinib arm and 4.2 months in the sunitinib arm. This corresponds to an absolute difference of 15.7 months.

A separate statement on additional benefit based on the sub-group analyses for the characteristic "region" is not made despite the observed effect modification. This is because the sub-group analysis is regarded as uncertain in the present data situation. The sub-group "Rest of the world" includes only 7 patients in the control arm and 11 patients in the intervention arm. Because of the sometimes very few patients per sub-group of the sub-population under consideration, there are relevant uncertainties as to the extent to which there is a sufficiently reliable data basis.

Against this background, in the present case, the total population is used for the derivation of the additional benefit. The effect modification by the characteristic "region" is nevertheless considered a relevant result of this benefit assessment.

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

Morbidity

Progression-free survival (PFS)

The endpoint PFS is defined as the time from randomisation to the first documentation of disease progression or to death by any cause, whichever comes 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 avelumab + axitinib (HR: 0.43 95% CI [0.27; 0.69]; p value: 0.0004). Disease progression occurred in 43 patients (47.2%) in the avelumab + axitinib arm and in 50 patients (70.4%) in the sunitinib arm.

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the Javelin Renal 101 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 (FKSI-DRS)

The disease symptomatology of the study participants was assessed with 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.

As a primary analysis, the pharmaceutical company presented an evaluation from a mixed model for repeated measurements (MMRM) for the mean change in disease-related symptoms (FKSI-DRS overall score) over the course of the study. In the evaluations submitted with the dossier, more than 10% of patients were completely absent. Moreover, contrary to the original planning in the Javelin Renal 101 study, only values collected under treatment were included in the MMRM evaluations.

In the written statement, the pharmaceutical company submitted further MMRM evaluations, which include all available survey dates even after therapy discontinuation. Thus, 90% of the randomised patients in the intervention arm and 83% in the control arm can be included in the evaluation.

There is a statistically significant difference between the study arms to the benefit of avelumab + axitinib. However, it cannot be derived with sufficient certainty that this is a clinically relevant effect.

As a further supporting analysis, the dossier included *post hoc* MMRM evaluations of further sub-scales of individual items of the FKSI-19 questionnaire (see also “Health-related quality of life” section). Because the sub-scales have not been validated and some of the individual items are already covered by the FKSI-DRS or do not represent the symptoms, the evaluations described are not considered for this assessment.

In the dossier, the pharmaceutical company also presented additional analyses in the form of evaluations of the time to the 1st deterioration as well as the time to the 1st final deterioration by a Minimal important Difference (MID) of 3 points. Although responder analyses based on an MID for a clinical assessment of effects have general advantages over an analysis of mean differences, the G-BA does not use the additional responder analyses submitted by the pharmaceutical company in this assessment to assess the effects on the symptomatology because the MID is not validated.

Health status (EQ-5D VAS)

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

As a primary analysis, the pharmaceutical company presented a MMRM evaluation for the mean change over the course of the study. Contrary to the original planning in the Javelin Renal 101 study, only values collected under treatment were included in the MMRM evaluations. Because the difference between the proportions of patients completely absent from the two arms in the MMRM evaluation of the EQ-5D VAS was greater than 15%, the data were not used in the dossier assessment of the IQWiG.

In the written statement, the pharmaceutical company submitted further MMRM evaluations, which include all available survey dates even after therapy discontinuation. Thus 90% of the randomised patients in the intervention arm and 80% in the control arm are included in the evaluation.

There is a statistically significant difference between the study arms to the benefit of avelumab + axitinib. However, it cannot be derived with sufficient certainty that this is a clinically relevant effect.

Overall, in the endpoint category morbidity, there are statistically significant differences in disease-specific symptomatology and health status between the treatment arms in favour of avelumab in combination with axitinib. However, it cannot be derived with sufficient certainty that these are clinically relevant effects.

Quality of life

For the assessment of health-related quality of life, the pharmaceutical company presented evaluations of the FKSI-19 measuring instrument. The FKSI-19 is a version of the disease-specific measuring instrument FKSI-15 extended by four questions. The disease-related symptomatology of patients with advanced renal carcinoma surveyed by the FKSI-15 is measured using the FKSI-DRS sub-scale and included in the endpoint category morbidity.

The 6 further questions of FKSI-15 that go beyond the FKSI-DRS are not suitable for a comprehensive view of the complex construct of health-related quality of life. Furthermore, for the FKSI-19, the criteria for selecting the 4 additional questions are not described, and the reliability of these items was not examined.

Against this background, the evaluation based on the FKSI-19 submitted by the pharmaceutical company are not used to assess the additional benefit in the endpoint category quality of life.

Side effects

In the Javelin Renal 101 study, the planned follow-up period for all endpoints in the side effects category was 90 days after the last dose of study medication or until the start of follow-up therapy for non-serious side effects (whichever occurred first). Contrary to the pre-specified procedure, for the benefit assessment, the pharmaceutical company submitted only evaluations of the side effects that included only events that occurred up to 30 days after the last dose of the study medication or up to the start of a follow-up therapy (if this occurred earlier).

Adverse events (AE) in total

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

Serious adverse events (SAE), severe AE (CTCAE grade ≥ 3), therapy discontinuations because of AE

For the endpoints SAE, severe AE (CTCAE grade ≥ 3), and therapy discontinuations because of AE, there are no statistically significant differences between the treatment arms.

Specific AE

Immune-mediated AE

In the Javelin Renal 101 study, a potential immune-mediated AE was initially identified using an *a priori* defined list of preferred terms. However, from the AE determined this way, only the following were regarded as immune-mediated AE:
- events in which additional treatment (e.g. with corticosteroids or hormone therapy) was administered and no clear alternative explanation for the AE other than immune-mediated aetiology was available
and/or
- events in which a histopathology/biopsy compatible with an immune-mediated mechanism was required.

The operationalisation of the endpoint immune-mediated AE chosen in the study is assessed as not sufficiently reliable because of the causal link to a successful treatment and the lack of a clear alternative aetiology because it does not guarantee that all immune-mediated AE are covered. The data on immune-mediated AE are thus not considered usable.

Other specific AE

For other specific AE, advantages and disadvantages of avelumab + axitinib compared with sunitinib can be identified.

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

This is in contrast to the disadvantages of combination therapy compared with sunitinib for the endpoints hypertension (PT, severe AE [CTCAE grade ≥ 3]) and hypothyroidism (PT, AE).

For the specific AE “infusion-related reactions”, there are no usable data because in the Javelin Renal 101 study, infusions were administered only in the avelumab + axitinib arm.

In the overall view of the results on side effects, there is no advantage or disadvantage for avelumab + axitinib compared with sunitinib. In specific adverse events, in detail there are advantages and disadvantages of combination therapy compared with sunitinib.

<u>Overall assessment</u>

For the assessment of the additional benefit of avelumab in combination with axitinib for first-line treatment in adult patients with advanced renal cell carcinoma with an unfavourable risk profile (IMDC score ≥ 3), results for the endpoint categories mortality, morbidity, and side effects based on the Javelin Renal 101 study are available.

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

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

In the endpoint category morbidity, evaluations for disease-specific symptoms using the measuring instrument FKSI-DRS and for health status using the EQ-5D VAS are available.

For disease-specific symptoms and health status, avelumab in combination with axitinib has been shown to have advantages over sunitinib. However, it cannot be derived with sufficient certainty that these are clinically relevant effects.

Health-related quality of life data have not been submitted. An assessment of the influence of avelumab in combination with axitinib on the quality of life of patients is therefore not possible.

In terms of side effects, avelumab in combination with axitinib has neither an advantage nor a disadvantage compared with sunitinib. In specific adverse events, in detail there are advantages and disadvantages of combination therapy compared with sunitinib.

In the overall view of the results presented on the patient-relevant endpoints, the clear advantage in overall survival is not offset by disadvantages in morbidity and side effects.

As a result, the G-BA found a considerable additional benefit for avelumab in combination with axitinib for the first-line treatment of adults with advanced renal cell carcinoma 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 Javelin Renal 101 study compared avelumab 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.

For the overall survival endpoint, there are uncertainties regarding the effect of avelumab in combination with axitinib because of the effect modifications by the characteristic “region”.

Because the pharmaceutical company deviated from the a priori planned procedure in the Javelin Real 101 studies when evaluating adverse events for the benefit assessment, there are further uncertainties.

Furthermore, because of the open study design, the results of the patient-reported endpoints in particular are to be regarded as potentially highly biased and thus of limited informative value.

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.

2.1.4 Summary of the assessment

This assessment relates to the benefit assessment of a new therapeutic indication for the active ingredient avelumab in combination with axitinib.

The therapeutic indication assessed here is as follows:

Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) (see section 5.1).

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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 Javelin Renal 101 study.

In overall survival, there was no statistically significant difference between the treatment arms.

For morbidity, evaluations for disease-specific symptomatology and health status are available. There are neither advantages nor disadvantages for combination therapy compared with sunitinib.

Health-related quality of life data have not been submitted. An assessment of the influence of avelumab in combination with axitinib on the quality of life of patients is therefore not possible.

For side effects, avelumab in combination with axitinib has a moderate disadvantage compared with sunitinib in terms of therapy discontinuation because of adverse events. For specific adverse events, in detail there are advantages and disadvantages of combination therapy compared with sunitinib.

There are uncertainties because of the still relatively low event numbers for the endpoint overall survival and the evaluation on side effects. These differ from the pre-specified evaluations of the Javelin Renal 101 study.

Overall, avelumab in combination with axitinib has a moderate disadvantage in terms of side effects because of therapy discontinuation because of adverse events. However, this does not reach a level that would justify a lower benefit.

In the overall view, the additional benefit of avelumab in combination with axitinib compared with sunitinib is not proven.

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 Javelin Renal 101 study.

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

For morbidity, evaluations for disease-specific symptomatology and health status are available. For disease-specific symptoms and health status, avelumab in combination with axitinib has been shown to have advantages over sunitinib. However, it cannot be derived with sufficient certainty that these are clinically relevant effects.

Health-related quality of life data have not been submitted. An assessment of the influence of avelumab in combination with axitinib on the quality of life of patients is therefore not possible.

In terms of side effects, avelumab in combination with axitinib has neither an advantage nor a disadvantage compared with sunitinib. For specific adverse events, in detail there are advantages and disadvantages of combination therapy compared with sunitinib.

Uncertainties remain in particular with regard to the results for the overall survival endpoint because of the effect modifications caused by the characteristic “region”. In addition, evaluations submitted for the side effects deviate from the pre-specified evaluations of the Javelin Renal 101 study.

Overall, the clear advantage in overall survival compared with sunitinib is not offset by the disadvantages in morbidity and side effects.

In the overall view, there is a hint for a considerable additional benefit of avelumab 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).

As part of the written statement procedure, the pharmaceutical company submitted a recalculation for the distribution of the target population according to risk profile. Taking this information into account, the result for a) patients with a favourable or intermediate risk profile (IMDC score 0–2) is (approx. 2,130–4,060 patients and b) patients with an unfavourable risk profile (IMDC score ≥ 3) is (approx. 1,340–2,540 patients. The recalculated lower limit of the SHI target population is within a plausible range despite the uncertainties. The recalculated upper limit represents an overestimation because patients who are ineligible for first-line therapy are considered.

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) of this resolution. 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 Bavencio® (active ingredient: avelumab) at the following publicly accessible link (last access: 5 May 2020):

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

Treatment with avelumab 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 avelumab:

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

The Javelin Renal 101 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.

This medicinal product was approved under “special conditions”. This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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				
Avelumab in combination with axitinib				
Avelumab	1 × per 14-day cycle	26.1	1	26.1
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			
	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				

(Continuation)

Nivolumab Ipilimumab	1 × per 21-day cycle	4	1	4
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)[7].

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					
Avelumab in combination with axitinib					
Avelumab	800 mg	800 mg	4 × 200 mg	26.1	104.4 × 200 mg
Axitinib	5 mg	10 mg	2 × 5 mg	365	730 × 5 mg

(Continuation)

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

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					
	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
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

(Continuation)

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					
Avelumab	1 CIS	€ 1,005.62	€ 1.77	€ 55.07	€ 948.78
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.

According to the product information of avelumab, before the first 4 infusions of avelumab, patients must be premedicated with an antihistamine and paracetamol.

The product information does not provide any further details on this, which is why it is not possible to quantify the necessary costs.

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 9 April 2019.

On 20 November 2019, the pharmaceutical company submitted a dossier for the benefit assessment of avelumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 20 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 avelumab.

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.

By letter dated 6 April 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by the IQWiG were submitted to the G-BA on 23 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	9 April 2019	Determination 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, Commissioning of the IQWiG with the supplementary assessment of documents
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