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 Nivolumab (new therapeutic indication: renal cell carcinoma, in combination with ipilimumab, first-line treatment)

of 15 August 2019

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

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

On 11 January 2019, nivolumab received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 No. 2a to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

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

“OPDIVO in combination with ipilimumab is indicated for first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see Section 5.1)”.

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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 15 May 2019, 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 nivolumab 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 evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of nivolumab.

In light of the above and taking into account the comments received and the oral hearing, the G-BA has arrived at the following assessment:

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

2.1.1 Approved therapeutic indication of nivolumab (OPDIVO®) in accordance with the product information

OPDIVO in combination with ipilimumab is indicated for first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (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 an intermediate risk profile (IMDC score 1–2)

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

[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.

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, aldesleukin, bevacizumab, cabozantinib, interferon alfa-2a, pazopanib, sunitinib, temsirolimus, and tivozanib are available for the treatment of advanced renal cell carcinoma in non-pretreated adults.

On 2. For the patients in the present 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:

- 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 the present indication.

Systematic reviews and recommendations from guidelines are available for first-line treatment of advanced renal cell carcinoma. Based on these, bevacizumab in

combination with interferon-alpha, pazopanib, sunitinib, or temsirolimus can be considered as therapy options.

In 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 nivolumab in terms of risk according to the IMDC score (IMDC score 1–2 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 at low or moderate risk. Based on the evidence provided, no superior therapeutic benefit can be derived for any of the three therapies mentioned. Therefore, combination therapy with bevacizumab and interferon-alpha, monotherapy with pazopanib, or monotherapy with sunitinib are equally suitable as an appropriate comparator therapy for patients at moderate risk (intermediate risk profile) according to IMDC criteria (IMDC score 1–2).

For patients at a high risk (poor risk profile, IMDC score ≥ 3), both temsirolimus and sunitinib are determined as appropriate comparator therapies based on the evidence provided. Systematic reviews that allow a comparison between temsirolimus and sunitinib are not available. The current German S3 guideline and the Spanish SEOM/SOGUG guideline primarily strongly recommend the use of temsirolimus for this patient group but also cite sunitinib as a treatment option.

The recommendation is based on a Phase III study in which high-risk patients were examined and showed 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 the “European Association of Urology” (EAU) and “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. In addition, 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. A preference for temsirolimus or sunitinib cannot be inferred overall; both treatment options are thus considered equally appropriate for

[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.

first-line therapy of patients with advanced renal cell carcinoma with a poor 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 found 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 an 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.

Sunitinib is an appropriate comparator therapy for patients with both intermediate and poor risk profiles. Patients with intermediate and poor risk profiles have a different prognosis and therapy response, which is reflected in significant differences in overall survival. In addition, the guidelines provide therapy recommendations separately according to risk profile, irrespective of the respective active ingredients. The G-BA therefore considers it appropriate to consider the patient populations separately in the benefit assessment despite the overlap of the appropriate comparator therapies for the active ingredient sunitinib depending on the IMDC score (IMDC score 1–2 and IMDC score ≥ 3).

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

2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score 1–2)

Indication of 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 an intermediate risk profile (IMDC score 1–2)

and

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

For the benefit assessment of nivolumab, the pharmaceutical company presented the randomised, open, multi-centre Phase III CheckMate 214 (CA209-214) study.

The study included adults with untreated advanced clear cell renal cell carcinoma stage IV (AJCC classification[5]). Patients were included regardless of their risk profile in accordance with IMDC score. Patients with non-clear-cell renal cell carcinoma or with Karnofsky index < 70% were not included in the study population.

1096 study participants in a 1:1 randomisation were assigned to treatment with nivolumab in combination with ipilimumab (nivolumab + ipilimumab, 550 patients) or the control arm with the appropriate comparator therapy sunitinib (546 patients).

Randomisation was stratified by region and IMDC score at the start of study (favourable vs intermediate vs poor, defined as presence of 0 vs 1 to 2 vs 3 to 6 risk factors in accordance with IMDC score).

With regard to the sub-populations of patients with intermediate and poor risk profiles relevant for the present benefit assessment, 334 patients were assigned to the nivolumab + ipilimumab arm and 333 patients to the sunitinib arm with regard to the intermediate risk profile. The number of study participants with a poor risk profile included 91 patients in the nivolumab + ipilimumab arm and 89 patients in the sunitinib arm. The mean age of the study participants was 61 years in the nivolumab + ipilimumab arm and 60 years in the sunitinib arm.

According to the pharmaceutical company, the European Medicines Agency (EMA) filed an application to change the approved dosage of nivolumab for first-line treatment of advanced renal cell carcinoma in parallel with the procedure to expand the indication for nivolumab + ipilimumab. In the opinion of the EMA, the two dosage regimens (not dependent or dependent on body weight) are comparable in terms of efficacy and safety in the present indication, which is why the weight-independent dosage of nivolumab in the maintenance or monotherapy phase was also adopted by the EMA for this new indication and finally approved.

Patients were treated until disease progression or unacceptable persistent toxicities occurred. In addition, both treatment groups were allowed to continue the study medication after progression of the disease provided that the investigator confirmed a clinical benefit and tolerance of the substance. Switching treatment in the course of the study (cross-over) was not possible.

The CheckMate 214 study was prematurely terminated because of the superiority of nivolumab + ipilimumab over sunitinib based on the results of the first planned interim overall survival analysis dated 7 August 2017 and is currently in the follow-up phase.

Against the background of these results, Amendment 14 (13 November 2017) in the follow-up phase made it possible to switch patients of the sunitinib arm who stopped receiving sunitinib to nivolumab + ipilimumab. According to the information provided by the pharmaceutical company following the oral hearing, 13 patients with an intermediate risk profile and no patients with a poor risk profile took advantage of the opportunity to switch treatment.

Of the patients with an intermediate risk profile, 48% in the nivolumab + ipilimumab arm received systemic follow-up therapy. In the sunitinib arm, 64% of patients received systemic follow-up treatment; nivolumab (36%), axitinib (23%), and everolimus (11%) were the most commonly used active ingredients. Of the patients with a poor risk profile, 44 % in the nivolumab + ipilimumab arm received systemic follow-up therapy. In the sunitinib arm, this

[5] American Joint Committee on Cancer

figure was 49% of patients; nivolumab (26%), axitinib (19%), and everolimus (11%) were the most commonly used.

The present benefit assessment is based on the results of the second planned interim analysis of overall survival of 6 August 2018 and thus covers approximately three years of the study prior to approval of treatment switching and approx. 10 months of the study thereafter.

The study will assess overall survival and endpoints on relapses, symptomatology, health status, health-related quality of life, and adverse events. Co-primary endpoints are overall survival, progression-free survival, and objective response rate. The final analysis of overall survival is still pending and is planned after 639 deaths.

Data on the contribution of the individual components of combination therapy with nivolumab + ipilimumab were not collected in the CheckMate 214 study, which is why some members of the Committee for Medicinal Products for Human Use (CHMP) formulated a divergent position with regard to the extension of the approval underlying the present benefit assessment[6]. Against this background, the EMA requires the pharmaceutical company to conduct a post-authorisation efficacy study (PAES). This will further clarify the contribution of ipilimumab to the efficacy and toxicity of the combination therapy of nivolumab + ipilimumab compared with nivolumab monotherapy in the present indication.

[6] EMA. CHMP assessment report: OPDIVO/ YERVOY, 15 November 2018.

Extent and probability of the additional benefit

a) Adult patients with untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score 1–2)

Mortality

Overall survival

Nivolumab in combination with ipilimumab provides a statistically significant overall survival benefit over sunitinib treatment (Hazard ratio (HR): 0.70 95% confidence interval (CI) [0.55; 0.88]; p value: 0.003). 124 events (37.1%) occurred in the nivolumab + ipilimumab arm, and 159 events (47.7%) occurred in the sunitinib arm. In the intervention arm, the median survival time has not yet been reached.

The final analysis of overall survival is still pending and is planned after a total of 639 deaths.

Based on the data from the dossier of the pharmaceutical company, statistically significant effect modifications for the endpoint overall survival are additionally shown for the characteristics “age” and “PD-L1 status”.

In the subgroup analyses on the characteristic “age”, a statistically significant difference to the advantage of nivolumab + ipilimumab is found between the treatment arms but only for patients < 65 years of age. For patients ≥ 65 years, there was no statistically significant difference between the intervention arm and the control arm.

When the influence of the characteristic “PD-L1 status” (</≥ 1%, </≥ 5%, </≥ 10%) on overall survival is considered separately, statistically significant advantages for nivolumab + ipilimumab compared with sunitinib are observed only for the sub-groups with a higher PD-L1 level (≥ 1%, ≥ 5%, ≥ 10%).

A separate statement on the additional benefit based on the sub-group analyses for the characteristics “age” and “PD-L1 status” is not made in the present case despite the observed effects.

Here it is taken into account that with regard to the sub-group characteristic “PD-L1 status”, there are still uncertainties regarding a possible limit value because of the temporal dynamics as well as the heterogeneous distribution of PD-L1 expression during the course of the disease.

Furthermore, the effects observed in overall survival related to both “age” and “PD-L1 status” are not consistent with effects seen for other endpoints.

For this reason, the additional benefit in overall survival is evaluated for the entire population.

The combination therapy of nivolumab and ipilimumab compared with sunitinib yields a significant improvement in overall survival.

Morbidity

Progression-free survival (PFS)

The endpoint PFS is operationalised as the period between the date of randomisation and the date of the first documented progression according to the Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) or the date of death of any cause, whichever occurs first. The results of the second planned interim analysis of 6 August 2018 on which the present benefit assessment is based are based on the information provided by the investigator.

For PFS, there is a statistically significant difference in favour of nivolumab + ipilimumab (HR: 0.816 95% CI [0.685; 0.972]; p value: 0.0217). The median time to event shows an absolute difference of 0.23 months (8.18 months vs 8.41 months). The proportion of patients with an event was higher in the sunitinib arm (81.7%) than in the intervention arm (71.6%).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component "mortality" was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging techniques (according to RECIST v1.1). 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-related symptomatology 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 nine questions on specific symptoms in patients with advanced renal carcinoma. The CheckMate 214 study prespecified use of FKSI-19 rather than FKSI-15. FKSI-19 is a version of FKSI-15 extended by four questions, whereby the selection criteria of the additional questions were not specified and their reliability was not examined.

The dossier evaluation of the IQWiG used the pharmaceutical company's primary analyses of the FKS-DRS in the form of the mean difference from a mixed model for repeated measurements (MMRM).

Based on the mean difference, a statistically significant improvement of the disease-related symptomatology for nivolumab + ipilimumab compared with sunitinib was observed (MD: 1.03 95% CI [0.58; 1.47]; p value: < 0.001). The improvement of symptomatology in patients treated with nivolumab + ipilimumab is to be assessed as clinically relevant because the 95% CI of the standardised mean difference (Hedges' g) is completely above the irrelevance range [−0.2; 0.2].

In addition, the pharmaceutical company submitted sensitivity analyses in the form of responder analyses with a Minimal Important Difference (MID) of ≥ 2 or ≥ 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 the present assessment to assess the effects on the symptomatology because the MID is not validated and the evaluation of the FKSI-15 or FKS-DRS was not pre-specified.

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company presented an *a priori* planned evaluation of the mean difference from an MMRM analysis as the primary analysis. Additional *post hoc* sensitivity studies were also carried out for the time until deterioration was confirmed in the form of responder analyses with an MID of ≥ 7 points and ≥ 10 points compared to baseline.

The responder analyses were not used in the IQWiG dossier evaluation because the study underlying the derivation of the MID (Pickard *et al.*, 2007[7]) was classified as unsuitable to validate the MID. This is justified on one hand by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. Furthermore, the anchors ECOG-Performance Status and FACT-G Sum Score used in the study are also not considered suitable to derive an MID.

Instead of the responder analyses, the evaluation of the mean difference using the MMRM analyses is used in the dossier evaluation of the IQWiG.

There is a statistically significant difference between the treatment arms in favour of nivolumab + ipilimumab. However, the differences observed are not clinically relevant

[7] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual. Life Outcomes* 2007; 5: 70.

because the 95% CI of the standardised mean difference (Hedges' g) is not completely outside the irrelevance range [−0.2; 0.2].

In view of the fact that there are general advantages in using MID-based responder analyses to clinically evaluate effects over analyses of differences in mean values and in view of the fact that the validation study in question has already been used in earlier evaluations, in the present assessment, the G-BA has decided to use the responder analyses up to the time of confirmed worsening by ≥ 7 points and ≥ 10 points to assess the effects on symptomatology.

There are no statistically significant differences between the treatment arms.

In summary, in the morbidity endpoint category the combination therapy of nivolumab + ipilimumab has a demonstrable advantage over sunitinib because of improvements in disease-related patient symptomatology.

Quality of life

FACT-G

Health-related quality of life was assessed using the generic FACT-G (Functional Assessment of Cancer Therapy - General) questionnaire. The questionnaire consists of 27 questions, which in turn are assigned to the four sub-scales physical well-being (PWB), emotional well-being (EWB), functional well-being (FWB), and social well-being (SWB). In addition to the overall score evaluations of the overall score, the pharmaceutical company also presented sub-scale scores. Only the FACT-G total score was considered in the assessment of additional benefit because this provides a comprehensive overview of the data on patients' health-related quality of life. The individual FACT-G sub-scales are therefore presented only on a supplementary basis. The evaluations are based on the mean difference using MMRM analyses.

For the FACT-G total score, there is a statistically significant advantage for the combination therapy of nivolumab + ipilimumab over treatment with sunitinib on the basis of the mean difference; this corresponds to an improvement in health-related quality of life (MD: 3.64 95% CI [2.05; 5.24]; p value: < 0.001). The improvement of the health-related quality of life is to be assessed as clinically relevant because the 95% CI of the standardised mean difference (Hedges' g) is completely above the irrelevance range [−0.2; 0.2].

For the endpoint category health-related quality of life, the pharmaceutical company also provided evaluations of the disease-specific measuring instrument FKSI-15, which in turn is based on FKSI-19. The evaluations of the FKSI-15 were not pre-specified. The disease-related symptomatology of patients with advanced renal carcinoma recorded by the FKSI-15 is measured using the FKSI-DRS sub-scale and included in the endpoint category morbidity. In turn, the questions of the FKSI-15 that go beyond the FKSI-DRS are not suitable for comprehensively investigating the health-related quality of life of patients. Therefore, taking into account the above aspects, the FKSI-15 is not used in assessing additional benefit in the quality of life endpoint category.

In summary, an advantage has been demonstrated for the combination therapy of nivolumab + ipilimumab compared to sunitinib on the basis of an improvement to health-related quality of life.

Side effects

Adverse events (AE) in total

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

Serious adverse events (SAE)

There is a statistically significant difference between the treatment arms to the detriment of nivolumab + ipilimumab (HR: 1.38 95% CI [1.11; 1.71]; p value: 0.004). The median time to

the occurrence of an SAE is 9.13 months in the intervention arm and 20.83 months in the control arm. An SAE therefore occurs 11.70 months (median) earlier under nivolumab + ipilimumab therapy than under sunitinib.

Severe AE (CTCAE grade 3–4)

For the endpoint severe AE (CTCAE grade 3–4), the pharmaceutical company submitted analyses in the benefit assessment dossier for the time up to the first occurrence and stated that the event with the highest severity was generally considered in the evaluation for this endpoint. Such operationalisation can lead to potentially biased outcomes.

In the written statement procedure, the pharmaceutical company clarified by explaining that in the event time analyses available in the dossier for the benefit assessment, the time up to the first occurrence of an AE of grade 3 or 4 was taken into account. Such an operationalisation is considered appropriate, which is why the event time analyses are used.

A statistically significant difference to the advantage of nivolumab + ipilimumab compared to sunitinib is shown (HR: 0.66 95% CI [0.55; 0.79]; p value: < 0.001). The median time to severe AE (CTCAE grade 3–4) is 2.14 months longer for nivolumab + ipilimumab (4.21 months) than for sunitinib (2.14 months).

Therapy discontinuation because of AE

For the endpoint therapy discontinuation because of AE, there is a statistically significant disadvantage for nivolumab + ipilimumab (HR: 1.51 95% CI [1.09; 2.09]; p value: 0.012).

Because only 95 events (28.5%) had occurred in the nivolumab + ipilimumab arm and 61 events (18.5%) in the sunitinib arm at the time of the data cut-off relevant for evaluation, the median time to an event had not been reached in both treatment arms.

Specific AE

For the endpoint specific AE, only evaluations of the proportion of patients with events at the system organ class level (SOC) and preferred designations (PT) for frequent AE, SAE, severe AE (CTCAE grade 3–4), and therapy discontinuations because of AE were provided by the pharmaceutical company in the benefit assessment dossier. Based on this, the IQWiG calculated its own relative risks in the dossier evaluation.

Within the framework of the written statement procedure, the pharmaceutical company submitted further evaluations in the form of event time analyses on the frequently occurring AE, SAE, severe AE (CTCAE grade 3–4), and therapy discontinuations because of AE. Because of the differences in the median treatment and observation durations between the study arms, these are regarded as a more suitable form of evaluation and used in the present evaluation.

With regard to specific adverse events, nivolumab + ipilimumab has advantages and disadvantages compared with sunitinib.

In detail, there are statistically significant differences in favour of nivolumab + ipilimumab in the AE gastrointestinal disorders, hand-foot syndrome, epistaxis, reduced appetite, taste disorder, and hypertension as well as blood and lymphatic system disorders.

In contrast, for the AE pruritus, rash, myalgia, and endocrine disorders, there are statistically significant differences to the detriment of nivolumab + ipilimumab compared with sunitinib.

Immune mediated AE

The operationalisation of the endpoint in the CheckMate 214 study, according to which immune mediated AE were assessed on the basis of selected AE and the administration of immunomodulating medications for immunosuppression, does not ensure that all immunomediated AE are mapped by the endpoint. As a result, the data submitted by the pharmaceutical company on the endpoint immune mediated AE are considered not to be usable.

Overall, the results on side effects show advantages and disadvantages for the combination therapy of nivolumab + ipilimumab compared with sunitinib. Advantages in the occurrence of severe adverse events (CTCAE grade 3–4) are offset by disadvantages because of serious adverse events and to therapy discontinuations resulting from adverse events. With regard to specific adverse events, nivolumab + ipilimumab have both advantages and disadvantages compared with sunitinib because of the different side effect profiles of the active ingredients.

Overall assessment

For the assessment of the additional benefit of nivolumab in combination with ipilimumab for first-line treatment of advanced renal cell carcinoma in adults with an intermediate risk profile (IMDC score 1–2), results are available for the endpoint categories mortality, morbidity, quality of life, and side effects.

The assessment is based on the CheckMate 214 study, which compared the combination therapy of nivolumab and ipilimumab with the appropriate comparator therapy sunitinib.

Treatment with nivolumab in combination with ipilimumab leads to a statistically significant advantage in overall survival over sunitinib. Because of effect modifications by the characteristics “PD-L1 status” and “age”, there are uncertainties regarding the observed effect on overall survival.

Further advantages of combination therapy over sunitinib can be seen in the endpoint categories morbidity and quality of life. Here, positive effects can be seen because of a reduction in disease-related symptomatology and an improvement in health-related quality of life.

In the side effects endpoint category, both positive and negative effects of combination therapy compared with sunitinib can be observed. The advantage for severe adverse events (CTCAE grade 3–4) is offset by disadvantages in the occurrence of serious adverse events and therapy discontinuations because of adverse events. In terms of specific adverse events, nivolumab in combination with ipilimumab has both advantages and disadvantages over sunitinib.

In an overall consideration of the available results on the patient-relevant endpoints, the G-BA comes to the conclusion in a weighing decision that the advantages in terms of overall survival, disease-related symptomatology, health-related quality of life, and severe adverse events outweigh the disadvantages in terms of serious side effects and therapy discontinuations. There is a significant improvement in the therapy-relevant benefit that has not yet been achieved.

As a result, the G-BA found that nivolumab in combination with ipilimumab for first-line treatment of advanced renal cell carcinoma in adults with an intermediate risk profile (IMDC score 1–2) has a considerable additional benefit.

Reliability of data (probability of additional benefit)

The randomised, open-label phase III CheckMate 214 study compared nivolumab in combination with ipilimumab with the appropriate comparator therapy sunitinib.

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.

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. However, the overall risk of bias at the endpoint level is not considered to be so high 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 to be low. The reliability of data supporting the finding of an additional benefit must therefore be classified as “indication”.

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

Mortality

Overall survival

Nivolumab in combination with ipilimumab provides a statistically significant overall survival benefit over sunitinib treatment (HR: 0.58 95% CI [0.41; 0.83]; p value: 0.003). The median survival time was extended by 11.73 months to a relevant extent by treatment with nivolumab + ipilimumab (21.45 months) compared with sunitinib (9.72 months).

The combination therapy consisting of nivolumab and ipilimumab thus leads to a significant improvement in overall survival compared with sunitinib.

Morbidity

Progression-free survival (PFS)

The endpoint PFS is operationalised as the period between the date of randomisation and the date of the first documented progression according to the Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) or the date of death of any cause, whichever occurs first. The results of the second planned interim analysis of 6 August 2018 on which the present benefit assessment is based are based on the information provided by the investigator.

For PFS, there is a statistically significant difference in favour of nivolumab + ipilimumab (HR: 0.599 95% CI [0.433; 0.829]; p value: 0.0018). Compared with sunitinib, the median time to an event was extended by 1.99 months (6.26 months vs 4.27 months). The proportion of patients with an event was also higher in the sunitinib arm (94.4%) than in the intervention arm (80.2%).

The PFS endpoint is a combined endpoint composed of endpoints of the mortality and morbidity categories. In the present study, the endpoint component “mortality” was collected as an independent endpoint via the endpoint overall survival. The morbidity component was not assessed on the basis of symptoms but rather exclusively using imaging techniques (according to RECIST v1.1). 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-related symptomatology 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 nine questions on specific symptoms in patients with advanced renal carcinoma. The CheckMate 214 study prespecified use of FKSI-19 rather than FKSI-15. FKSI-19 is a version of FKSI-15 extended by four questions, whereby the selection criteria of the additional questions were not specified and their reliability was not examined.

The dossier evaluation of the IQWiG used the pharmaceutical company’s primary analyses of the FKS-DRS in the form of the mean difference from a mixed model for repeated measurements (MMRM).

For the mean difference, there is no statistically significant difference between the intervention arm and the control arm.

In addition, the pharmaceutical company submitted sensitivity analyses in the form of responder analyses with a MID of ≥ 2 or ≥ 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 the present assessment to assess the effects on the symptomatology because the MID is not validated and the evaluation of the FKSI-15 or FKS-DRS was not pre-specified.

Health status (EQ-5D VAS)

Health status was assessed using the visual analogue scale (VAS) of the EQ-5D questionnaire. For the benefit assessment, the pharmaceutical company presented an a priori planned evaluation of the mean difference from an MMRM analysis as the primary analysis. Additional *post hoc* sensitivity studies were also carried out at the time until deterioration was confirmed in the form of responder analyses with a MID of ≥ 7 points and ≥ 10 points compared to baseline.

The responder analyses were not used in the IQWiG dossier evaluation because the study underlying the derivation of the MID (Pickard *et al.*, 2007[7]) was classified as unsuitable to validate the MID. This is justified on one hand by the fact that the work mentioned does not contain a longitudinal study to determine the MID, which is assumed in the current scientific discussion on deriving a valid MID. Furthermore, the anchors ECOG-Performance Status and FACT-G Sum Score used in the study are also not considered suitable to derive an MID.

Instead of the responder analyses, the evaluation of the mean difference using the MMRM analyses is used in the dossier evaluation of the IQWiG. There is no statistically significant difference between the treatment arms.

In view of the fact that there are general advantages in using MID-based responder analyses to clinically evaluate effects over analyses of differences in mean values and in view of the fact that the validation study in question has already been used in earlier evaluations, in the present assessment, the G-BA has decided to use the responder analyses up to the time of confirmed worsening by ≥ 7 points and ≥ 10 points to assess the effects on symptomatology.

There are no statistically significant differences between the treatment arms.

In summary, the endpoint category morbidity for the combination therapy of nivolumab + ipilimumab shows neither advantages nor disadvantages compared with sunitinib.

Quality of life

Health-related quality of life was assessed using the generic FACT-G questionnaire. The questionnaire consists of 27 questions, which in turn are assigned to the four sub-scales physical well-being (PWB), emotional well-being (EWB), functional well-being (FWB), and social well-being (SWB). In addition to the overall score evaluations of the overall score, the pharmaceutical company also presented sub-scale scores. Only the FACT-G total score was considered in the assessment of additional benefit because this provides a comprehensive overview of the data on patients' health-related quality of life. The individual FACT-G sub-scales are therefore presented only on a supplementary basis. The evaluations are based on the mean difference using MMRM analyses.

For the FACT-G total score, there is no statistically significant difference between the treatment arms.

For the endpoint category health-related quality of life, the pharmaceutical company also provided evaluations of the disease-specific measuring instrument FKSI-15, which in turn is based on FKSI-19. The evaluations of the FKSI-15 were not pre-specified. The disease-related symptomatology of patients with advanced renal carcinoma recorded by the FKSI-15 is measured using the FKSI-DRS sub-scale and included in the endpoint category morbidity. In turn, the questions of the FKSI-15 that go beyond the FKSI-DRS are not suitable for comprehensively investigating the health-related quality of life of patients. Therefore, taking into account the above aspects, the FKSI-15 is not used in assessing additional benefit in the quality of life endpoint category.

In summary, for the combination therapy of nivolumab + ipilimumab, there are neither advantages nor disadvantages in the endpoint category of health-related quality of life compared with sunitinib.

Side effects

Adverse events (AE) in total

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

Serious AE (SAE), therapy discontinuation because of AE

For the endpoints SAE and therapy discontinuation because of AE, there is no statistically significant difference between the treatment arms.

Severe AE (CTCAE grade 3–4)

For the endpoint severe AE (CTCAE grade 3–4), the pharmaceutical company submitted analyses in the benefit assessment dossier for the time up to the first occurrence and stated that the event with the highest severity was generally considered in the evaluation for this endpoint. Such operationalisation can lead to potentially biased outcomes.

In the written statement procedure, the pharmaceutical company clarified by explaining that in the event time analyses available in the dossier for the benefit assessment, the time up to the first occurrence of an AE of grade 3 or 4 was taken into account. Such an operationalisation is considered appropriate, which is why the event time analyses are used.

A statistically significant difference to the advantage of nivolumab + ipilimumab compared to sunitinib is shown (HR: 0.57 95% CI [0.41; 0.81]; p value: 0.001). The median time to severe AE (CTCAE grade 3–4) is 1.41 months longer for nivolumab + ipilimumab (2.76 months) than for sunitinib (1.35 months).

For the endpoint severe AE (CTCAE grade 3–4), there is an effect modification by the characteristic “age” (< 65 years / ≥ 65 years to < 75 years / ≥ 75 years). The subgroup analysis shows a statistically significant advantage of nivolumab + ipilimumab between the treatment arms but only for patients ≥ 65 years to < 75 years and ≥ 75 years. For patients < 65 years, there was no statistically significant difference between the intervention arm and the control arm.

There is no consistency of effects across other endpoints.

Therefore, the overall additional benefit for the endpoint severe AE is assessed on the basis of a common population.

Specific AE

For the endpoint specific AE, only evaluations of the proportion of patients with events at the system organ class level (SOC) and preferred designations (PT) for frequent AE, SAE, severe AE (CTCAE grade 3–4), and therapy discontinuations because of AE were provided by the pharmaceutical company in the benefit assessment dossier. Based on this, the IQWiG calculated its own relative risks in the dossier evaluation.

Within the framework of the written statement procedure, the pharmaceutical company submitted further evaluations in the form of event time analyses on the frequently occurring AE, SAE, severe AE (CTCAE grade 3–4), and therapy discontinuations because of AE. Because of the differences in the median treatment and observation durations between the study arms, these are regarded as a more suitable form of evaluation and used in the present evaluation.

With regard to specific adverse events, nivolumab + ipilimumab has advantages and disadvantages compared with sunitinib.

In detail, there are statistically significant differences in favour of nivolumab + ipilimumab for the AE stomatitis, mucositis, epistaxis, hand-foot syndrome, taste disorder, respiratory, thoracic, and mediastinal disorders, hypothyroidism, gastrointestinal disorders, thrombocytopenia, and hypertension.

In contrast, for the AE fever and pruritus, there are statistically significant differences to the detriment of nivolumab + ipilimumab compared with sunitinib.

Immune mediated AE

The operationalisation of the endpoint in the CheckMate 214 study, according to which immune mediated AE were assessed on the basis of selected AE and the administration of immunomodulating medications for immunosuppression, does not ensure that all immunomediated AE are mapped by the endpoint. As a result, the data submitted by the pharmaceutical company on the endpoint immune mediated AE are considered not to be usable.

Overall, the results on side effects show an advantage for the combination therapy of nivolumab + ipilimumab compared with sunitinib because of positive effects with respect to severe adverse events (CTCAE grade 3–4). With regard to specific adverse events, nivolumab + ipilimumab have both advantages and disadvantages compared with sunitinib.

Overall assessment

For the assessment of the additional benefit of nivolumab in combination with ipilimumab in first-line treatment of advanced renal cell carcinoma in adults with a poor risk profile (IMDC score ≥ 3), results are available for the endpoint categories mortality, morbidity, quality of life, and side effects.

The assessment is based on the CheckMate 214 study, which compared the combination therapy of nivolumab and ipilimumab with the appropriate comparator therapy sunitinib.

Treatment with nivolumab in combination with ipilimumab leads to a statistically significant prolongation of overall survival compared with sunitinib. The median extension by 11.73 months is regarded as a so far unachieved significant improvement.

With regard to the other endpoint categories of morbidity and quality of life, no advantage or disadvantage can be identified for treatment with nivolumab in combination with ipilimumab compared to sunitinib.

In terms of side effects, the combination therapy has been shown to be advantageous over the appropriate comparator therapy because of the reductions in severe adverse events (CTCAE grade 3–4). For specific adverse events, both advantages and disadvantages of nivolumab in combination with ipilimumab compared with sunitinib can be observed.

In an overall consideration of the available results on the patient-relevant endpoints, the significant prolongation of overall survival and the benefit in terms of side effects compared with sunitinib are not offset by disadvantages in terms of morbidity and health-related quality of life.

As a result, the G-BA finds that nivolumab in combination with ipilimumab for first-line treatment of advanced renal cell carcinoma in adults with a poor risk profile (IMDC score ≥ 3) has a considerable additional benefit.

Reliability of data (probability of additional benefit)

The randomised, open-label phase III CheckMate 214 study compared nivolumab in combination with ipilimumab with the appropriate comparator therapy sunitinib.

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.

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. However, the overall risk of bias at the endpoint level is not considered to be so high 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 to be 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

The present assessment concerns the benefit assessment of the active ingredient nivolumab in combination with ipilimumab in a new therapeutic indication:

"OPDIVO in combination with ipilimumab is indicated for first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma".

In the benefit assessment, two patient groups were distinguished:

a) Adult patients with untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score 1–2)

and

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

On patient group a)

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

- Bevacizumab in combination with interferon alfa-2a

  or
- Monotherapy with pazopanib

  or
- Monotherapy with sunitinib

For the benefit assessment, the pharmaceutical company presented the randomised, open, multi-centre Phase III CheckMate 214 (CA209-214) study in which nivolumab in combination with ipilimumab was compared with sunitinib, the appropriate comparator therapy.

The CheckMate 214 study was prematurely terminated because of the superiority of nivolumab in combination with ipilimumab over sunitinib and is currently in the follow-up phase.

Nivolumab in combination with ipilimumab is clearly advantageous in overall survival compared with sunitinib. Because of effect modifications by the characteristics "PD-L1 status" and "age", there are uncertainties regarding the observed effect.

Other advantages of combination therapy compared with sunitinib are a reduction in disease-related symptomatology and an improvement in health-related quality of life.

In terms of side effects, there are both positive and negative effects of the combination therapy compared with sunitinib. The advantage for severe adverse events (CTCAE grade 3–4) is offset by the disadvantages for serious adverse events and therapy discontinuations because of adverse events. In terms of specific adverse events, nivolumab in combination with ipilimumab has both advantages and disadvantages over sunitinib.

In a balancing decision, the G-BA has concluded that the advantages outweigh the disadvantages.

In the overall view, there is an indication of a considerable additional benefit.

On patient group b)

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

- Sunitinib

  or

- Temsirolimus

For the benefit assessment, the pharmaceutical company presented the randomised, open, multi-centre Phase III CheckMate 214 (CA209-214) study in which nivolumab in combination with ipilimumab was compared with sunitinib, the appropriate comparator therapy.

The CheckMate 214 study was prematurely terminated because of the superiority of nivolumab in combination with ipilimumab over sunitinib and is currently in the follow-up phase.

Nivolumab in combination with ipilimumab is clearly advantageous in overall survival compared with sunitinib.

Neither in the endpoint category morbidity nor quality of life is there any advantage or disadvantage for combination therapy compared with sunitinib.

With regard to side effects, the combination therapy has an advantage over the appropriate comparative therapy because of the positive effects with respect to severe adverse events (CTCAE grade 3–4). In terms of specific adverse events, nivolumab in combination with ipilimumab has both advantages and disadvantages over sunitinib.

Overall, the significant prolongation of overall survival and the benefit in terms of side effects compared with sunitinib are not offset by disadvantages in terms of morbidity and health-related quality of life.

In the overall view, there is an indication of a considerable additional benefit.

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 resolution will be based on the information from the dossier of the pharmaceutical company.

However, the patient numbers derived by the pharmaceutical company are subject to uncertainties, in particular because of the procedure for deriving the risk distribution. Accordingly, in the publications used to determine the proportions of patients with advanced renal cell carcinoma and an intermediate/poor risk profile, different proportions are reported, especially for the group with a poor risk profile.

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 OPDIVO® (active ingredient: nivolumab) at the following publicly accessible link (last access: 25 June 2019):

https://www.ema.europa.eu/documents/product-information/opdivo-epar-product-information_en.pdf

Only specialists in internal medicine, haematology, and oncology with experience treating patients with advanced renal cell carcinoma, specialists in internal medicine and nephrology, and doctors from other specialisms participating in the oncology agreement may initiate and monitor treatment with nivolumab in combination with ipilimumab.

In accordance with the specifications of the EMA regarding additional measures for risk minimisation, the pharmaceutical company must provide training material for doctors as well as a patient card. The training and information material shall include, in particular, instructions on how to deal with the immune-mediated adverse reactions potentially occurring with nivolumab. Patients treated with nivolumab must be informed about the risks of treatment with nivolumab.

The CheckMate 214 (CA209-214) 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 July 2019).

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 period:

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

Designation of the therapy	Treatment mode
Medicinal product to be assessed	
Nivolumab in combination with ipilimumab	
Initial treatment	
Nivolumab	1 x per 21-day cycle
Ipilimumab	
Follow-up treatment	
Nivolumab	1 x per 14-day cycle (3 weeks after last do treatment)
	or
	1 x per 28-day cycle (6 weeks after last do treatment)
Appropriate comparator therapy	
a) Adult patients with untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score	
Bevacizumab in combination with interferon alfa-2a	
Bevacizumab	1 x every 2 weeks
Interferon alfa-2a	3 x per week
Monotherapies	
Pazopanib	1 x daily
Sunitinib	28 x per 42-day cycle
b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)	
Temsirolimus	1 x per week
Sunitinib	28 x per 42-day cycle

Usage and consumption:

For dosages depending on body weight (BW), 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 kg)[8].

[8] Statistisches Bundesamt [German Federal Office for Statistics] Microcensus 2017: *Questions on health; body measurements of the population 2017* [online]. 2 August 2018 [Accessed: 11 September 2018]. URL: https://www.destatis.de/DE/Publikationen/Thematisch/Gesundheit/Gesundheitszustand/Koerpermasse5239003179004.pdf?__blob=publicationFile

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Nivolumab in combination with ipilimumab					
Initial treatment					
Nivolumab	3 mg/kg BW	231 mg	2 × 100 mg 1 x 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	40 x 100 mg 20 x 40 mg
	or				
	480 mg	480 mg	4 × 100 mg 2 × 40 mg	10	40 × 100 mg 20 × 40 mg
Appropriate comparator therapy					
a) Adult patients with untreated advanced renal cell carcinoma with an intermediate risk profile (IMDC score 1–2)					
Bevacizumab in combination with interferon alfa-2a					
Bevacizumab	10 mg/kg BW	770 mg	2 × 400 mg	26	52 × 400 mg
Interferon alfa-2a	9 million I.U.	9 million I.U.	1 × 9 million I.U.	156	156 × 9 million I.U.
Monotherapies					
Pazopanib	800 mg	800 mg	2 × 400 mg	365	730 × 400 mg
Sunitinib	50 mg	50 mg	1 × 50 mg	224	224 × 50 mg
b) Adult patients with untreated advanced renal cell carcinoma with a poor risk profile (IMDC score ≥ 3)					
Temsirolimus	25 mg	25 mg	1 × 30 mg	52	52 × 30 mg
Sunitinib	50 mg	50 mg	1 × 50 mg	224	224 × 50 mg

Costs:

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

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Nivolumab	1 vial, 40 mg	€ 523.06	€ 1.77	€ 28.35	€ 492.94
Nivolumab	1 vial, 100 mg	€ 1,291.17	€ 1.77	€ 70.88	€ 1,218.52
Ipilimumab	1 vial, 50 mg	€ 3,811.46	€ 1.77	€ 214.40	€ 3,595.29
Appropriate comparator therapy					
Bevacizumab in combination with interferon alfa-2a					
Bevacizumab	1 IFK, 400 mg	€ 1,689.80	€ 1.77	€ 93.23	€ 1,594.80
Interferon alfa-2a	30 PS, 9 million I.U.	€ 3,153.33	€ 1.77	€ 176.81	€ 2,974.75
Monotherapies					
Pazopanib	60 FCT, 400 mg	€ 4,740.67	€ 1.77	€ 267.47	€ 4,471.43
Sunitinib	30 HC, 50 mg	€ 7,214.01	€ 1.77	€ 408.72	€ 6,803.52
Temsirolimus	1 IFK, 30 mg	€ 1,182.80	€ 1.77	€ 64.88	€ 1,116.15
Abbreviations: PS = prefilled syringes, IFK = concentrate for the preparation of an infusion solution, FCT = film-coated tablets, HC = hard capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 July 2019

Costs for additionally required SHI services:

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

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the usual 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 SHI services:

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

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

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 6 February 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 4 February 2019, the pharmaceutical company submitted a dossier for the benefit assessment of nivolumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2, sentence 2 VerfO.

By letter dated 5 February 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 nivolumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 May 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 15 May 2019. The deadline for submitting written statements was 5 June 2019.

The oral hearing was held on 24 June 2019.

By letter dated 24 June 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 19 July 2019.

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

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 6 August 2019, and the proposed resolution was approved.

At its session on 15 August 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	6 February 2018	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	10 December 2018	Redefinition of the appropriate comparator therapy
Working group Section 35a	18 June 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	24 June 2019	Conduct of the oral hearing, Commissioning of the Institute for Quality and Efficiency in Health Care (IQWiG) with supplementary assessment of documents
Working group Section 35a	3 July 2019 17 July 2019 31 July 2019	Advice on the dossier evaluation of the Institute for Quality and Efficiency in Health Care (IQWiG), evaluation of the written statement procedure
Subcommittee Medicinal product	6 August 2019	Concluding discussion of the proposed resolution
Plenum	15 August 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 August 2019

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

Prof Hecken