IQWiG Reports – Commission No. A19-99

Pembrolizumab (renal cell carcinoma) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Pembrolizumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 December 2019.

Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab in combination with axitinib (hereinafter referred to as "pembrolizumab + axitinib") in comparison with the appropriate comparator therapy (ACT) in treatment-naive adult patients with advanced renal cell carcinoma.

The research questions presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab + axitinib

Research question	Subindication	ACT[a]
1	Treatment-naive adult patients with advanced renal cell carcinoma with favourable or intermediate risk profile (0–2 risk factors of the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or monotherapy with **sunitinib**
2	Treatment-naive adult patients with advanced renal cell carcinoma with poor risk profile (≥ 3 risk factors of the IMDC criteria)	Temsirolimus or **sunitinib**

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

The company followed the G-BA's specification of the ACT and chose sunitinib from the options presented for both research questions. Deviating from the G-BA, the company considered the patients together as one patient population regardless of their risk profile. Concurring with the G-BA's specification, the present assessment was conducted for both research questions 1 and 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Study pool and risk of bias for research questions 1 and 2

Study pool and study characteristics

The study pool for the benefit assessment of pembrolizumab + axitinib in comparison with the ACT consisted of the study KEYNOTE-426.

The KEYNOTE-426 study is a randomized, open-label, active-controlled approval study on the comparison of pembrolizumab + axitinib with sunitinib. The study included adults with advanced or metastatic clear-cell renal cell carcinoma (Stage IV according to the American Joint Committee on Cancer [AJCC] classification). The patients were not allowed to have received any prior systemic therapy for advanced disease; any adjuvant or neoadjuvant therapy had to be completed 12 months before the start of the study. The patients had to be in good general condition (Karnofsky performance status ≥ 70%).

Overall, 861 patients were randomly allocated in a 1:1 ratio either to treatment with pembrolizumab + axitinib (N = 432) or to sunitinib (N = 429). Treatment with pembrolizumab + axitinib and sunitinib was in compliance with the recommendations provided in the Summaries of Product Characteristics (SPCs).

Patients were included in the study regardless of their risk profile according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score. The company presented separate analyses on patients with favourable or intermediate risk profile (0–2 risk factors of the IMDC criteria, concurring with research question 1), and on patients with poor risk profile (≥ 3 risk factors of the IMDC criteria, concurring with research question 2).

Primary outcomes of the study were overall survival and progression-free survival (PFS). Patient-relevant secondary outcomes were symptoms, health status, health-related quality of life and adverse events (AEs).

Risk of bias

The risk of bias across outcomes was rated as low for the results of the study. With the exception of overall survival, the risk of bias for the results of other outcomes was rated as high. The reason for this was, on the one hand, the open-label study design and, on the other, the incomplete observations for potentially informative reasons.

No usable data were available for the outcomes of symptoms (recorded with the symptom scales of the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire-Core 30 [QLQ-C30] and of the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]), of health status (measured with the European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]) and of health-related quality of life (recorded with the functional scales of the EORTC QLQ-C30), so that the risk of bias for the results on these outcomes was not assessed.

Results for research question 1: patients with favourable or intermediate risk profile

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Morbidity

Symptoms (recorded with the EORTC QLQ-C30 symptom scales)

There were no usable data for the outcome "symptoms" recorded with the EORTC QLQ-C30 symptom scales. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Symptoms (recorded with the FKSI-DRS)

There were no usable data for the outcome "symptoms" recorded with the FKSI-DRS. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health status (recorded with the EQ-5D VAS)

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (recorded with the EORTC QLQ-C30 functional scales)

There were no usable data for the outcome "health-related quality of life" recorded with the EORTC QLQ-C30 functional scales. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference to the disadvantage of pembrolizumab + axitinib was shown between the treatment arms for the outcome "serious AEs (SAEs)". This resulted in a hint of greater harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for the outcome "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)". Hence,

there was no hint of greater/lesser harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome; an added benefit is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab + axitinib was shown between the treatment arms for the outcome "discontinuation due to AEs". This resulted in a hint of greater harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab + axitinib between the treatment arms was shown for each of the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". Due to the large effect in each case, high certainty of results was assumed despite the high risk of bias. This resulted in an indication of greater harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes.

Respiratory, thoracic and mediastinal disorders (System Organ Class [SOC], AEs), endocrine disorders (SOC, SAEs), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of pembrolizumab + axitinib was shown between the treatment arms for each of the following outcomes: respiratory, thoracic and mediastinal disorders, endocrine disorders, hepatobiliary disorders, and renal urinary disorders. This resulted in a hint of greater harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes.

Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for each of the outcomes "blood and lymphatic system disorders" and "infections and infestations". This resulted in a hint of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for the outcome "infections and infestations". Due to the large effect, high certainty of results was assumed for the outcome "blood and lymphatic system disorders" despite the high risk of bias. This resulted in an indication of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Results for research question 2: patients with poor risk profile

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Morbidity

Symptoms (recorded with the EORTC QLQ-C30 symptom scales)

There were no usable data for the outcome "symptoms" recorded with the EORTC QLQ-C30 symptom scales. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Symptoms (recorded with the FKSI-DRS)

There were no usable data for the outcome "symptoms" recorded with the FKSI-DRS. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health status (recorded with the EQ-5D VAS)

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (recorded with the EORTC QLQ-C30 functional scales)

There were no usable data for the outcome "health-related quality of life" recorded with the EORTC QLQ-C30 functional scales. Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between the treatment arms was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from pembrolizumab + axitinib in comparison with sunitinib; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference between the treatment arms in favour of pembrolizumab + axitinib was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Discontinuation due to AEs

No statistically significant difference between the treatment arms was shown for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome; greater or lesser harm is therefore not proven.

Immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for each of the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". This resulted in no hint of greater or lesser harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes; greater or lesser harm is therefore not proven.

Nervous system disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), general disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for each of the following outcomes: nervous system disorders, blood and lymphatic system disorders, general disorders and administration site conditions, and metabolism and nutrition disorders. This resulted in a hint of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, probability and extent of the added benefit of pembrolizumab + axitinib in comparison with the ACT are assessed as follows:

Research question 1: patients with favourable or intermediate risk profile

Overall, positive and negative effects were shown.

On the side of positive effects, there was an indication of major added benefit of pembrolizumab + axitinib for the outcome "overall survival". Furthermore, positive effects with the probability "hint" or "indication" and the extent "minor" or "major" were shown in the outcome category of serious/severe side effects.

On the side of negative effects, several hints with different extent were shown for side effects, and 2 indications, each with major extent, in the outcome category of serious/severe side effects. Overall, the negative effects of pembrolizumab + sunitinib did not call into question the positive effects, but they did lead to a downgrading of the extent.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

In summary, there is an indication of considerable added benefit of pembrolizumab + axitinib versus sunitinib for treatment-naive adult patients with advanced renal cell carcinoma with favourable or intermediate risk profile.

Research question 2: patients with poor risk profile

Overall, only positive effects with different probability and extent were shown for pembrolizumab + axitinib in comparison with sunitinib. The indication of considerable added benefit of pembrolizumab + axitinib for the outcome "overall survival" was decisive for the overall conclusion on the added benefit. This was supported by the positive effects in the outcome category of side effects.

In summary, there is an indication of considerable added benefit of pembrolizumab + axitinib versus the ACT for treatment-naive adult patients with advanced renal cell carcinoma with poor risk profile.

Table 3 shows a summary of probability and extent of the added benefit of pembrolizumab + axitinib.

Table 3: Pembrolizumab + axitinib – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
1	Treatment-naive adult patients with advanced renal cell carcinoma with favourable or intermediate risk profile (0–2 risk factors of the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or monotherapy with **sunitinib**	Indication of considerable added benefit[b]
2	Treatment-naive adult patients with advanced renal cell carcinoma with poor risk profile (≥ 3 risk factors of the IMDC criteria)	Temsirolimus or **sunitinib**	Indication of considerable added benefit[b]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The KEYNOTE-426 study did not investigate patients with non-clear cell renal cell carcinoma or with Karnofsky performance status < 70%. It remains unclear whether the observed effects can be transferred to these patients.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of pembrolizumab + axitinib in comparison with the ACT in treatment-naive adult patients with advanced renal cell carcinoma.

The research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab + axitinib

Research question	Subindication	ACT[a]
1	Treatment-naive adult patients with advanced renal cell carcinoma with favourable or intermediate risk profile (0–2 risk factors of the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or monotherapy with **sunitinib**
2	Treatment-naive adult patients with advanced renal cell carcinoma with poor risk profile (≥ 3 risk factors of the IMDC criteria)	Temsirolimus or **sunitinib**

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

The company followed the G-BA's specification of the ACT and chose sunitinib from the options presented for both research questions. Deviating from the G-BA, the company considered the patients together as one patient population regardless of their risk profile (see Section 2.7.2 of the full dossier assessment). Concurring with the G-BA's specification, the present assessment was conducted for both research questions 1 and 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

2.3 Research question 1: patients with favourable or intermediate risk profile

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on pembrolizumab + axitinib (status: 7 October 2019)
- bibliographical literature search on pembrolizumab + axitinib (last search on 1 October 2019)
- search in trial registries for studies on pembrolizumab + axitinib (last search on 2 October 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 6 December 2019)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
KEYNOTE-426	Yes	Yes	No
a. Study for which the company was sponsor.			
RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of pembrolizumab + axitinib in comparison with the ACT consisted of the KEYNOTE-426 study and concurred with that of the company.

The KEYNOTE-426 study included patients with favourable or intermediate risk profile as well as those with poor risk profile.

The company derived the added benefit regardless of the risk profile on the basis of the results of the total study population. The company did not provide separate information on the added benefit for the respective relevant subpopulations of research questions 1 (patients with favourable or intermediate risk profile) and 2 (patients with poor risk profile).

The benefit assessment included the results of the subpopulation with favourable or intermediate risk profile (IMDC score 0–2, corresponding to the presence of 0–2 risk factors according to the IMDC score) for research question 1, and the results of the subpopulation with poor risk profile (IMDC score ≥ 3, corresponding to the presence of at least 3 risk factors according to the IMDC score) for research question 2. The added benefit of pembrolizumab + axitinib was derived separately for both patient populations. This was possible because the company provided also separate analyses for the subpopulations of research questions 1 and 2 in Module 4 C as supplementary information.

Section 2.6 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the study for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KEYNOTE-426	RCT, open-label, parallel	Treatment-naive adult patients with advanced or metastatic clear-cell[b] renal cell carcinoma (AJCC Stage IV)	Pembrolizumab + axitinib (N = 432) sunitinib (N = 429) Relevant subpopulations thereof: Research question 1: patients with favourable or intermediate risk profile pembrolizumab + axitinib (n = 376) sunitinib (n = 377) Research question 2: patients with poor risk profile pembrolizumab + axitinib (n = 56) sunitinib (n = 52)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity or treatment discontinuation following the decision by the physician or the patient; pembrolizumab was not allowed to be administered for more than 35 cycles[c] Observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	124 study centres in Brazil, Canada, Czech Republic, France, Germany, Great Britain, Hungary, Ireland, Japan, Poland, Russia, South Korea, Spain, Taiwan, Ukraine, USA 10/2016–ongoing Data cut-offs: ▪ 24 August 2018 (prespecified, first interim analysis) ▪ 2 January 2019 (post hoc)[e]	Primary: overall survival, PFS Secondary: symptoms, health status, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. In addition to patients with clear-cell renal cell carcinoma, patients with a clear-cell component were also included (research question 1: 7% each in the pembrolizumab + axitinib arm and in the sunitinib arm; research question 2: 4% in the pembrolizumab + axitinib arm and 2% in the sunitinib arm).
c. With a complete, confirmed response or after reaching the maximum treatment duration in stable disease, patients after subsequent confirmed progression could resume treatment with pembrolizumab for another year ("second course phase").
d. Outcome-specific information is provided in Table 8.
e. Upon request by the EMA.

AE: adverse event; AJCC: American Joint Committee on Cancer; EMA: European Medicines Agency; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib

Study	Intervention	Comparison
KEYNOTE-426	Pembrolizumab 200 mg IV as 30-minute infusion every 3 weeks for a maximum of 35 cycles + axitinib 5 mg orally 2x daily	Sunitinib 50 mg orally daily, continuous cycles: 4 weeks of administration, 2-week rest period
	Dose adjustments: Pembrolizumab: ▪ no dose adjustment allowed ▪ treatment interruption (for a maximum of 3 weeks) due to AEs allowed Axitinib: ▪ if no AEs occur, dose increase to 7 mg after 6 weeks and to 10 mg after another 6 weeks allowed ▪ in case of AEs, dose reduction to 3 mg and 2 mg or treatment interruption	Dose adjustments: ▪ in case of AEs, treatment interruption and/or dose reduction in 12.5 mg steps to 25 mg ▪ dose increase in 12.5 mg steps to a maximum of 75 mg allowed
	Permitted pretreatment ▪ adjuvant or neoadjuvant therapy > 12 months before start of study **Non-permitted pretreatment** ▪ major surgery ≤ 4 weeks before start of study ▪ radiotherapy ≤ 2 weeks before start of study ▪ treatment with antibodies against anti-PD-1, anti-PD-L1, anti-PD-L2 or any other immune-regulatory receptors/mechanisms ▪ systemic anti-cancer therapy (e.g. VEGF/VEGFR inhibitors, chemotherapy) ▪ immunosuppressive drugs ≤ 7 days before start of study **Non-permitted concomitant treatment** ▪ other antineoplastic therapy ▪ live vaccine < 30 days before start of study until 30 days after the last dose of pembrolizumab ▪ antiarrhythmics (only in the sunitinib arm) ▪ systemic corticosteroids (> 7 days) except for the treatment of AEs or as premedication of chemotherapy or in case of contrast agent intolerance (only in the pembrolizumab + axitinib arm)	

AE: adverse event; IV: intravenous; PD: programmed cell death; PD-L1: programmed cell death ligand 1; PD-L2: programmed cell death ligand 2; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; VEGFR: VEGF receptor; vs.: versus

Study design

The KEYNOTE-426 study is a randomized, open-label, active-controlled approval study on the comparison of pembrolizumab + axitinib with sunitinib. The study included adults with advanced or metastatic clear-cell renal cell carcinoma (Stage IV according to the AJCC classification). The patients were not allowed to have received any prior systemic therapy for

advanced disease; any adjuvant or neoadjuvant therapy had to be completed 12 months before the start of the study. The patients had to be in good general condition (Karnofsky performance status ≥ 70%). Patients with non-clear cell renal cell carcinoma, with a Karnofsky performance status < 70% or with active brain metastases were excluded from participation in the study; hence, no data are available for them.

Patients regardless of their risk profile were included in the study. However, the IMDC score in the study was recorded as a disease characteristic at the beginning of the study so that it is possible to differentiate patients based on their risk profile according to the IMDC score. The IMDC score contains 6 risk factors. Based on the number of risk factors present in the patients, patients are assigned to the risk profiles according to the IMDC score:

- favourable risk profile (0 risk factors)
- intermediate risk profile (1–2 risk factors)
- poor risk profile (≥ 3 risk factors)

In Module 4 C, the company derived the added benefit regardless of the risk profile on the basis of the results of the total study population. For the benefit assessment, however, patients with a favourable or intermediate (research question 1) or poor risk profile (research question 2) were considered as separate subpopulations in accordance with the G-BA's specification of the ACT.

Overall, 861 patients were randomly allocated in a 1:1 ratio either to treatment with pembrolizumab + axitinib (N = 432) or to sunitinib (N = 429). Randomization was stratified by region (North America versus Western Europe versus rest of the world) and risk profile according to IMDC score [3] (favourable versus intermediate versus poor) at baseline.

The company presented analyses of the relevant subpopulations. For the subpopulation with favourable and intermediate risk profile (research question 1), these were 376 patients in the pembrolizumab + axitinib arm and 377 patients in the sunitinib arm. The subpopulation with poor risk profile (research question 2) comprised 56 patients in the pembrolizumab + axitinib arm and 52 patients in the sunitinib arm. The analyses of this subpopulation presented by the company were used for the benefit assessment (see also Section 2.4).

Treatment with pembrolizumab + axitinib was in accordance with the regimen described in Table 7 and was in compliance with the recommendations provided in the SPCs [4-6].

Primary outcomes of the study were overall survival and PFS. Patient-relevant secondary outcomes were symptoms, health status, health-related quality of life and AEs.

Patients were treated until disease progression, the occurrence of unacceptable, persistent toxicity or discontinuation of therapy at the decision of the physician or study participant. Treatment in the intervention arm was restricted by the maximum number of allowed cycles

(35 cycles) of pembrolizumab. It is unclear whether this number was reached by patients at the time point of the second data cut-off (2 September 2019). At the time point of the first data cut-off (24 August 2018), the patients had received an average of 14 cycles of pembrolizumab. The minimum was 1 cycle, the maximum 31 cycles; due to the short time period between the data cut-offs, it cannot be assumed that a relevant proportion of patients had already reached 35 cycles at the time point of the second data cut-off.

After discontinuation of the study medication, there were no restrictions regarding subsequent therapies. 22% of the patients with favourable and intermediate risk profile (research question 1) in the pembrolizumab + axitinib arm received subsequent systemic therapy, compared with 37% in the sunitinib arm (see Table 35 in Appendix C of the full dossier assessment). In the subpopulation with poor risk profile (research question 2), 34% of the patients in the pembrolizumab + axitinib arm received subsequent systemic therapy, compared with 44% in the sunitinib arm (see Table 36 in Appendix C of the full dossier assessment). In compliance with the Guideline on Diagnostics, Therapy and Follow-up of Renal Cell Carcinoma [7], besides nivolumab, subsequent therapy in the comparator arm also included cabozantinib; the guideline does not contain any recommendations regarding subsequent therapy for the intervention arm.

Switching to the treatment of the respective other study arm was not allowed in the course of the study.

Data cut-offs

The KEYNOTE-426 study is still ongoing. So far, results on 2 data cut-offs are available:

- first data cut-off (24 August 2018): prespecified first interim analysis on reaching 305 events in the outcome “PFS” and after at least 7 months of follow-up observation of all patients after randomization
- second data cut-off (2 January 2019): data cut-off conducted post hoc upon request by the European Medicines Agency (EMA)

In Module 4 C, the company presented analyses for all patient-relevant outcomes on both data cut-offs. The second data cut-off was used for the present benefit assessment.

Follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
KEYNOTE-426	
Mortality	
Overall survival	After progression, start of a new antineoplastic therapy or discontinuation of the study medication every 12 weeks until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, FKSI-DRS)	Until 30 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	Until 30 days after the last dose of the study medication
Side effects	
AEs and severe AEs	Until 30 days after the last dose of the study medication
SAEs	Until 90 days after the last dose of the study medication or until 30 days after the last dose of the study medication if a new antineoplastic therapy is started

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes in the categories “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days or 90 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile) (multipage table)

Study Characteristics Category	**Pembrolizumab + axitinib N = 376**	**Sunitinib N = 377**
KEYNOTE-426		
Age [years], mean (SD)	62 (10)	61 (10)
Sex [F/M], %	30/70	25/75
Family origin, n (%)		
White	298 (79.3)	297 (78.8)
Non-white	71 (18.9)	75 (19.9)
Missing	7 (1.9)	5 (1.3)
Region, n (%)		
North America	93 (24.7)	90 (23.9)
Western Europe	87 (23.1)	89 (23.6)
Rest of the world	196 (52.1)	198 (52.5)
Karnofsky performance status, n (%)		
90/100	313 (83.2)	313 (83)
70/80	62 (16.5)	64 (17)
Missing	1 (0.3)	0 (0)
IMDC risk profile		
Favourable	138 (36.7)	131 (34.7)
Intermediate	238 (63.3)	246 (65.3)
PD-L1 status[a], n (%)		
CPS < 1	148 (39.4)	143 (37.9)
CPS ≥ 1	209 (55.6)	221 (58.6)
Not reported	19 (5.1)[b]	13 (3.4)[b]
Number of organs affected by metastasis at baseline, n (%)		
1	109 (29.0)	88 (23.3)
≥ 2	264 (70.2)	287 (76.1)
Missing	3 (0.8)	2 (0.5)
Renal cell carcinoma with sarcomatoid features, n (%)		
Yes	41 (10.9)	48 (12.7)
No	209 (55.6)	218 (57.8)
Not reported	126 (33.5)[b]	111 (29.4)[b]
Disease status at start of study, n (%)		
Recurrent	230 (61.2)	217 (57.6)
Newly diagnosed	146 (38.8)	160 (42.4)
Prior nephrectomy, n (%)		
Yes	327 (87.0)	327 (86.7)
No	49 (13.0)	50 (13.3)
Treatment discontinuation, n (%)	178 (47.6)[c]	232 (62.2)
Study discontinuation, n (%)	ND	ND

Table 9: Characteristics of the study population – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile) (multipage table)

Study Characteristics Category	Pembrolizumab + axitinib N = 376	Sunitinib N = 377

a. Method of analysis unclear.
b. Institute's calculation.
c. Information refers to discontinuation of pembrolizumab + axitinib.

CPS: combined positive score; F: female; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; M: male; n: number of patients in the category; N: number of randomized patients in the subpopulation with favourable or intermediate risk profile; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and clinical characteristics of the patients with favourable or intermediate risk profile are balanced between the study arms. The majority of the study participants were male, which is due to the higher disease rate in men [8]. The mean age of the patients was 61 years and most were of white family origin. The majority of the patients in both study arms were in good general condition (Karnofsky performance status of ≥ 90). About 60% of the patients had recurrent disease at baseline. The number of treatment discontinuations was higher in the sunitinib arm (62%) than in the pembrolizumab + axitinib arm (48%). The most common reasons for discontinuation were disease progression and AEs. In the total population, 51% of the patients in the pembrolizumab + axitinib arm and 58% of the patients in the sunitinib arm discontinued due to disease progression; the figures for discontinuations due to AEs were 30% and 24%, respectively. There was no information for the subpopulations and for study discontinuation.

Course of the study

Table 10 shows the mean and median treatment duration and the mean and median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + axitinib** **N = 374**	**Sunitinib** **N = 373**
KEYNOTE-426		
Treatment duration [months]		
Median [Q1; Q3]	14.3 [8.1; 18.6]	11.3 [4.9; 16.1]
Mean (SD)	13.5 (6.6)	10.9 (6.9)
Observation period [months]		
Overall survival[a], morbidity, health-related quality of life	ND	ND
Side effects (AEs)		
Median [Q1; Q3]	14.4 [9.1; 18.9]	11.9 [5.9; 16.6]
Mean (SD)	13.9 (6.3)	11.6 (6.7)
Side effects (SAEs)		
Median [Q1; Q3]	14.9 [10.5; 19.1]	12.8 [7.10; 17.5]
Mean (SD)	14.7 (5.7)	12.7 (6.2)

a. For the total study population, the median observation period was 17.2 months in the intervention arm and 15.5 months in the control arm.

AE: adverse event; ASaT: all subjects as treated; N: number of analysed patients in the subpopulation with favourable or intermediate risk profile (ASaT); ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

With 14 months, the median treatment duration was longer in the pembrolizumab + axitinib arm in comparison with the sunitinib arm with 11 months. Information for the outcomes "morbidity" and "health-related quality of life" is neither available for the total population nor for the subpopulations. These outcomes were to be observed until 30 days after treatment discontinuation. It can be inferred from this that the observation periods for these outcomes were longer in the pembrolizumab + axitinib arm than in the sunitinib arm. The median observation period for AEs in the pembrolizumab + axitinib arm was 2.5 months longer than in the sunitinib arm; and 2.1 months longer for SAEs.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
KEYNOTE-426	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the study. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms (EORTC QLQ-C30 symptom scale)
  - symptoms (FKSI-DRS)
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life (EORTC QLQ-C30 functional scale)
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - SAEs and severe AEs (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 C) (see Section 2.7.4.3.2 of the full dossier assessment).

Table 12 shows for which outcomes data were available in the included KEYNOTE-426 study.

Table 12: Matrix of outcomes – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib

Study	Outcomes										
	Overall survival	**Symptoms (EORTC QLQ-C30)**	**Symptoms (FKSI-DRS)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (EORTC QLQ-C30)**	**SAEs[a]**	**Discontinuation due to AEs[a]**	**Severe AEs (CTCAE grade ≥ 3)[a]**	**Immune-related SAEs**	**Immune-related severe AEs (CTCAE grade ≥ 3)**	**Further specific AEs[b]**
KEYNOTE-426	Yes	No[c]	No[c]	No[c]	No[c]	Yes	Yes	Yes	Yes	Yes	Yes

a. Analysis without the PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression".

b. The following events (MedDRA coding) are considered for research question 1: respiratory, thoracic and mediastinal disorders (SOC, AEs), endocrine disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]), renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3]); and for research question 2: nervous system disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), general disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3]).

c. No usable data available due to unequal documentation times in the study arms; see Section 2.7.4.3.2 of the full dossier assessment for further justification.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib

Study	Study level	Outcomes										
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs[a]	Discontinuation due to AEs[a]	Severe AEs (CTCAE grade ≥ 3)[a]	Immune-related SAEs	Immune-related severe AEs (CTCAE grade ≥ 3)	Further specific AEs[b]
KEYNOTE-426	L	L	-[c]	-[c]	-[c]	-[c]	H[d]	H[e]	H[d]	H[d]	H[d]	H[d, f]

a. Analysis without the PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression".
b. The following events (MedDRA coding) are considered for research question 1: respiratory, thoracic and mediastinal disorders (SOC, AEs), endocrine disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3]), renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3]); and for research question 2: nervous system disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), general disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3]).
c. No usable data available due to unequal documentation times in the study arms; see Section 2.7.4.3.2 of the full dossier assessment for further justification.
d. Incomplete observations for potentially informative reasons.
e. Lack of blinding in subjective decision for discontinuation.
f. Despite high risk of bias, high certainty of results is assumed in research question 1 for the following outcomes: immune-related SAEs, immune-related severe AEs (CTCAE grade ≥ 3), and blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]) (see Section 2.7.4.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias for the result on the outcome "overall survival" was rated as low. This concurs with the company's assessment.

No usable data were available for the outcomes of symptoms (recorded with the symptom scales of the EORTC QLQ-C30 and of the FKSI-DRS), of health status (measured with the EQ-5D VAS) and of health-related quality of life (recorded with the functional scale of the EORTC

QLQ-C30) (see Section 2.7.4.3.2 of the full dossier assessment); the risk of bias for these outcomes was therefore not assessed.

The risk of bias of the result on the outcome "discontinuation due to AEs" was rated as high due to the open-label study design. For the other outcomes of the category "side effects", the risk of bias of the results was high due to incomplete observations for potentially informative reasons (see Section 2.7.4.2 of the full dossier assessment). This concurs with the company's assessment.

2.3.2.3 Results

Table 14 summarizes the results on the comparison of pembrolizumab + axitinib with sunitinib in treatment-naive adult patients with favourable or intermediate risk profile. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The available Kaplan-Meier curves on the event time analyses used are presented in Appendix A, the common AEs in Appendix B of the full dossier assessment.

Table 14: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile) (multipage table)

Study **Outcome category** **Outcome**	**Pembrolizumab + axitinib**		**Sunitinib**		**Pembrolizumab + axitinib vs. sunitinib**
	N	**Median time to event in months[a] [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months[a] [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
KEYNOTE-426					
Mortality					
Overall survival	376	NA 58 (15.4)	377	NA 90 (23.9)	0.57 [0.41; 0.80]; 0.001
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales)				No usable data[c]	
Symptoms (FKSI-DRS)				No usable data[c]	
Health status (EQ-5D VAS)				No usable data[c]	
Health-related quality of life					
Health-related quality of life (EORTC QLQ-C30 functional scales)				No usable data[c]	
Side effects					
AEs (supplementary information)[d]	*374*	*0.2 [0.2; 0.3]* *370 (98.9)*	*373*	*0.3 [0.3; 0.4]* *373 (100.0)*	–
SAEs[d]	374	19.2 [15.1; NC] 167 (44.7)	373	24.2 [24.2; NC] 123 (33.0)	1.36 [1.08; 1.72]; 0.009
Severe AEs (CTCAE grade ≥ 3)[d]	374	3.1 [2.8; 3.9] 298 (79.7)	373	2.4 [2.0; 3.4] 271 (72.7)	1.02 [0.87; 1.20]; 0.801
Discontinuation due to AEs[d]	374	NA[e] 127 (34.0)	373	NA 53 (14.2)	2.40 [1.74; 3.31]; < 0.001

Table 14: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile) (multipage table)

Study Outcome category Outcome	Pembrolizumab + axitinib N	Pembrolizumab + axitinib Median time to event in months[a] [95% CI] Patients with event n (%)	Sunitinib N	Sunitinib Median time to event in months[a] [95% CI] Patients with event n (%)	Pembrolizumab + axitinib vs. sunitinib HR [95% CI]; p-value[b]
Immune-related AEs (supplementary information)[f]	*374*	*8.3 [5.7; 12.0]* *208 (55.6)*	*373*	*16.5 [12.5; 20.9]* *151 (40.5)*	–
Immune-related SAEs	374	NA 42 (11.2)	373	NA 5 (1.3)	7.80 [3.08; 19.71]; < 0.001
Immune-related severe AEs (CTCAE grade ≥ 3)	374	NA 47 (12.6)	373	NA 6 (1.6)	7.10 [3.03; 16.61]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	374	5.8 [4.0; 8.3] 233 (62.3)	373	20.8 [15.0; NC] 155 (41.6)	1.70 [1.38; 2.08]; < 0.001
Endocrine disorders (SOC, SAEs)	374	NA 12 (3.2)	373	NA 1 (0.3)	11.02 [1.43; 84.78]; 0.021
Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3])	374	NA 5 (1.3)	373	NA 72 (19.3)	0.06 [0.02; 0.14]; < 0.001
Hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3])	374	NA 24 (6.4)	373	NA 10 (2.7)	2.24 [1.07; 4.69]; 0.032
Infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3])	374	NA 32 (8.6)	373	NA 45 (12.1)	0.61 [0.39; 0.96]; 0.032
Renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3])	374	NA 32 (8.6)	373	NA 14 (3.8)	2.20 [1.17; 4.12]; 0.014

a. Data for side effects: Institute's calculation (weeks in months).
b. HR; CI and p-value: Cox proportional hazards model; for the outcome "overall survival" stratified by region (North America vs. Western Europe vs. rest of the world); for the outcomes of the category "side effects" unstratified.
c. No usable data available due to unequal documentation times in the study arms; see Section 2.7.4.3.2 of the full dossier assessment for further justification.
d. Analysis without the PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression".
e. It is not clear from the documents whether this refers to discontinuation of pembrolizumab and/or axitinib.
f. In the total population of the study, mainly the PTs "hyperthyroidism" and "hypothyroidism" are included in the outcome at the time point of the first data cut-off. For 30 (about 55%) patients in the intervention arm versus 13 (about 81%) patients in the comparator arm, events based on CTCAE grade 1 were included for hyperthyroidism, and for 49 (32%) vs. 55 (41%) patients for hypothyroidism. CTCAE grade 1 is not patient-relevant for these PTs, as it is defined as "asymptomatic; clinical or diagnostic observations only; intervention not indicated" [9,10]. Information for the second data cut-off is not available.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome "overall survival". There was a high risk of bias of the results for the other outcomes; an outcome-specific high certainty of results may be assumed, however (see result description below). The company derived the added benefit exclusively on the basis of the total study population. For this reason, similarities or deviations in comparison with the assessment of the added benefit by the company are not commented on below.

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Morbidity

Symptoms (recorded with the EORTC QLQ-C30 symptom scales)

There were no usable data for the outcome "symptoms" recorded with the EORTC QLQ-C30 symptom scales (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Symptoms (recorded with the FKSI-DRS)

There were no usable data for the outcome "symptoms" recorded with the FKSI-DRS (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health status (recorded with the EQ-5D VAS)

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (recorded with the EORTC QLQ-C30 functional scales)

There were no usable data for the outcome "health-related quality of life" recorded with the EORTC QLQ-C30 functional scales (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference to the disadvantage of pembrolizumab + axitinib was shown between the treatment arms for the outcome "SAEs". This resulted in a hint of greater harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in no hint of greater or lesser harm from pembrolizumab + axitinib in comparison with sunitinib; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of pembrolizumab + axitinib was shown between the treatment arms for the outcome "discontinuation due to AEs". This resulted in a hint of greater harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of pembrolizumab + axitinib between the treatment arms was shown for each of the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". Due to the large effect, high certainty of results was assumed despite the high risk of bias (see Section 2.7.4.2 of the full dossier assessment). This resulted in an indication of greater harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes.

Respiratory, thoracic and mediastinal disorders (SOC, AEs), endocrine disorders (SOC, SAEs), hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3]), renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference to the disadvantage of pembrolizumab + axitinib was shown between the treatment arms for each of the following outcomes: respiratory, thoracic and mediastinal disorders, endocrine disorders, hepatobiliary disorders, and renal urinary disorders. This resulted in a hint of greater harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes.

Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for each of the outcomes "blood and lymphatic system disorders" and "infections and infestations". This resulted in a hint of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for the outcome "infections and infestations". Due to the large effect, high certainty of results was assumed for the outcome "blood and lymphatic system

disorders" despite the high risk of bias (see Section 2.7.4.2 of the full dossier assessment). This resulted in an indication of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics prespecified in the KEYNOTE-426 study were considered in the benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- region (North America versus Western Europe versus rest of the world)

Furthermore, the subgroup characteristic "disease severity according to IMDC score" was investigated in the KEYNOTE-426 study. Since the benefit assessment was already conducted separately for the patient populations with favourable or intermediate risk profile (research question 1) and with poor risk profile (research question 2) according to IMDC score, this characteristic is not additionally considered.

Interaction tests were performed if at least 10 patients per subgroup were included in the analysis. For binary data, there had to be 10 events in at least one subgroup.

Only results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the outcomes of the category "side effects", the dossier contained analyses on subgroup characteristics for the relevant second data cut-off only for the following outcomes: SAEs, discontinuation due to AEs, severe AEs (CTCAE grade ≥ 3), immune-related SAEs and severe immune-related AEs (CTCAE grade ≥ 3).

Table 15 presents the results of the subgroup analyses of pembrolizumab + axitinib in comparison with sunitinib.

Table 15: Subgroups (side effects) – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile)

Study Outcome Characteristic Subgroup	Pembrolizumab + axitinib N	Pembrolizumab + axitinib Median time to event in months[a] [95% CI] Patients with event n (%)	Sunitinib N	Sunitinib Median time to event in months[a] [95% CI] Patients with event n (%)	Pembrolizumab + axitinib vs. sunitinib HR [95% CI][b]	Pembrolizumab + axitinib vs. sunitinib p-value[b]
KEYNOTE-426						
Side effects						
Severe AEs (CTCAE grade ≥ 3)[c]						
Sex						
Male	263	3.2 [2.8; 4.4] 208 (79.1)	281	3.7 [2.5; 5.2] 194 (69.0)	1.15 [0.95; 1.40]	0.159
Female	111	2.8 [1.4; 4.2] 90 (81.1)	92	1.0 [0.9; 1.6] 77 (83.7)	0.64 [0.47; 0.87]	0.004
Total					Interaction:	0.002[d]
Region						
North America	91	2.1 [1.4; 3.0] 80 (87.9)	89	3.1 [2.1; 5.2] 60 (67.4)	1.50 [1.07; 2.10]	0.017
Western Europe	87	2.8 [2.1; 2.9] 77 (88.5)	87	1.6 [1.0; 3.2] 76 (87.4)	0.93 [0.68; 1.28]	0.661
Rest of the world	196	4.7 [3.5; 6.8] 141 (71.9)	197	2.4 [2.0; 4.1] 135 (68.5)	0.91 [0.72; 1.16]	0.457
Total					Interaction:	0.045[d]

a. Institute's calculation (weeks in months).
b. HR; CI and p-value: Cox proportional hazards model, unstratified.
c. Analysis without the PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression".
d. Q test.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; vs.: versus

Side effects

Severe AEs (CTCAE grade ≥ 3)

There were effect modifications for the outcome "severe AEs (CTCAE grade ≥ 3)" both by sex and by region. Since no information is available on a possible cross-interaction of the 2 effect modifiers, the result of the subgroup analyses cannot be interpreted. The result of the total population was used.

2.3.3 Probability and extent of added benefit

Probability and extent of added benefit for treatment-naive patients with advanced renal cell carcinoma and favourable or intermediate risk profile (research question 1) are derived below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.2 (see Table 16).

Determination of the outcome category for the outcomes on side effects

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Discontinuation due to AEs

There is no information for the allocation of the severity grade category for the outcome "discontinuation due to AEs". Therefore, the outcome "discontinuation due to AEs" was assigned to the category of non-serious/non-severe side effects.

Respiratory, thoracic and mediastinal disorders (SOC, AEs)

At the time point of the first data cut-off (24 August 2018), the events that had occurred in the specific AE "respiratory, thoracic and mediastinal disorders" were mostly non-serious. This information refers to the total populations; information for the subpopulation of patients with favourable or intermediate risk profile at the time point of the second data cut-off is not available. The outcome was therefore allocated to the outcome category "non-serious/non-severe side effects".

Table 16: Extent of added benefit at outcome level: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + axitinib vs. sunitinib** **Median time to event** **HR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. NA HR: 0.57 [0.41; 0.80]; p = 0.001 probability: "indication"	Outcome category: mortality $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Symptoms (EORTC QLQ-C30 symptom scales)	No usable data	Lesser benefit/added benefit not proven
Symptoms (FKSI-DRS)	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
Health-related quality of life (EORTC QLQ-C30 functional scales)	No usable data	Lesser benefit/added benefit not proven
Side effects		
SAEs	19.2 vs. 24.2 months HR: 1.36 [1.08; 1.72]; HR[c]: 0.74 [0.58; 0.93]; p = 0.009 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)	3.1 vs. 2.4 months HR: 1.02 [0.87; 1.20]; p = 0.801	Greater/lesser harm not proven
Discontinuation due to AEs	NA vs. NA HR: 2.40 [1.74; 3.31]; HR[c]: 0.42 [0.30; 0.57]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Immune-related SAEs	NA vs. NA HR: 7.80 [3.08; 19.71]; HR[c]: 0.13 [0.05; 0.32]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Immune-related severe AEs (CTCAE grade ≥ 3)	NA vs. NA HR: 7.10 [3.03; 16.61]; HR[c]: 0.14 [0.06; 0.33]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"

Table 16: Extent of added benefit at outcome level: pembrolizumab + axitinib vs. sunitinib (research question 1: patients with favourable or intermediate risk profile) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + axitinib vs. sunitinib** **Median time to event** **HR [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	5.8 vs. 20.8 months HR: 1.70 [1.38; 2.08]; HR[c]: 0.59 [0.48; 0.72]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Endocrine disorders (SOC, SAEs)	NA vs. NA HR: 11.02 [1.43; 84.78]; HR[c]: 0.09 [0.01; 0.70]; p = 0.021 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk < 5% greater harm, extent: "considerable"
Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3])	NA vs. NA HR: 0.06 [0.02; 0.14]; p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"
Hepatobiliary disorders (SOC, severe AEs [CTCAE grade ≥ 3])	NA vs. NA HR: 2.24 [1.07; 4.69]; HR[c]: 0.45 [0.21; 0.93]; p = 0.032 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Infections and infestations (SOC, severe AEs [CTCAE grade ≥ 3])	NA vs. NA HR: 0.61 [0.39; 0.96]; p = 0.032 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Renal and urinary disorders (SOC, severe AEs [CTCAE grade ≥ 3])	NA vs. NA HR: 2.20 [1.17; 4.12]; HR[c]: 0.45 [0.24; 0.85]; p = 0.014 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

a. Probability provided if a statistically significant and relevant effect is present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of pembrolizumab + axitinib in comparison with sunitinib (research question 1: patients with favourable or intermediate risk profile)

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of added benefit – extent: "major"	-
Serious/severe side effects ▪ Severe AEs (CTCAE grade ≥ 3): ▫ blood and lymphatic system disorders: indication of lesser harm – extent: "major" ▫ infections and infestations: hint of lesser harm – extent: "minor"	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "minor" ▪ Immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3): in each case indication of greater harm – extent: "major" ▪ Endocrine disorders (SAEs)[a]: hint of greater harm – extent: "considerable" ▪ Severe AEs (CTCAE grade ≥ 3): ▫ hepatobiliary disorders: hint of greater harm – extent: "minor" ▫ renal and urinary disorders: hint of greater harm – extent: "considerable"
-	Non-serious/non-severe side effects ▪ Discontinuation due to AEs; hint of greater harm – extent: "considerable" ▪ Respiratory, thoracic and mediastinal disorders (AEs): hint of greater harm – extent: "considerable"
There are no usable data for the outcomes on morbidity and health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).	
a. The SOC "endocrine disorders" is also represented by the immune-related events. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event; SOC: System Organ Class	

Overall, positive and negative effects were shown.

On the side of positive effects, there was an indication of major added benefit of pembrolizumab + axitinib for the outcome "overall survival". Furthermore, positive effects with the probability "hint" or "indication" and the extent "minor" or "major" were shown in the outcome category of serious/severe side effects.

On the side of negative effects, several hints with different extent were shown for side effects, and 2 indications, each with major extent, in the outcome category of serious/severe side effects. Overall, the negative effects of pembrolizumab + sunitinib did not call into question the positive effects, but they did lead to a downgrading of the extent.

In summary, there is an indication of considerable added benefit of pembrolizumab + axitinib versus sunitinib for treatment-naive adult patients with advanced renal cell carcinoma with favourable or intermediate risk profile.

The assessment described above deviates from that of the company, which derived an indication of a major added benefit for the total patient population in the therapeutic indication regardless of the risk profile. The company did not provide separate information on the added benefit for the relevant subpopulation of patients with favourable or intermediate risk profile (research question 1 of the present benefit assessment) (see Section 2.7.2 of the full dossier assessment).

2.4 Research question 2: patients with poor risk profile

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on pembrolizumab + axitinib (status: 7 October 2019)
- bibliographical literature search on pembrolizumab + axitinib (last search on 1 October 2019)
- search in trial registries for studies on pembrolizumab + axitinib (last search on 2 October 2019)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 6 December 2019)

No additional relevant study was identified from the check.

2.4.1.1 Studies included

The study pool for research question 2 of the benefit assessment of pembrolizumab + axitinib consisted of the RCT KEYNOTE-426 (see Table 5 in Section 2.3.1.1) and concurred with the study pool of the company.

The results of the subpopulation with poor risk profile (≥ 3 risk factors of the IMDC score) from this study were used for research question 2. This relevant subpopulation comprised 56 patients in the pembrolizumab + axitinib arm and 52 patients in the sunitinib arm.

The company derived the added benefit regardless of the risk profile on the basis of the results of the total study population. The company did not provide separate information on the added benefit for the subpopulation of research question 2 of the benefit assessment.

Section 2.6 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 6 and Table 7 in Section 2.3.1.2 describe the KEYNOTE-426 study. The study design and the available data cut-offs are also described in Section 2.3.1.2.

The planned follow-up observation is presented in Table 8 for the individual outcomes.

Characteristics of the study population

Table 18 shows the characteristics of the patients with poor risk profile in the included study.

Table 18: Characteristics of the study population – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 2: patients with poor risk profile)

Study Characteristics Category	**Pembrolizumab + axitinib N = 56**	**Sunitinib N = 52**
KEYNOTE-426		
Age [years], mean (SD)	59 (9)	59 (11)
Sex [F/M], %	21/79	29/71
Family origin, n (%)		
White	45 (80.4)	44 (84.6)
Non-white	9 (16.1)	8 (15.4)
Missing	2 (3.6)	0 (0)
Region, n (%)		
North America	11 (19.6)	13 (25.0)
Western Europe	19 (33.9)	15 (28.8)
Rest of the world	26 (46.4)	24 (46.2)
Karnofsky performance status, n (%)		
90/100	34 (60.7)	28 (53.8)
70/80	22 (39.3)	24 (46.2)
PD-L1 status[a], n (%)		
CPS < 1	19 (33.9)	15 (28.8)
CPS ≥ 1	33 (58.9)	33 (63.5)
Not reported	4 (7.1)[b]	4 (7.7)[b]
Number of organs affected by metastasis at baseline, n (%)		
1	5 (8.9)	8 (15.4)
≥ 2	51 (91.1)	44 (84.6)
Renal cell carcinoma with sarcomatoid features, n (%)		
Yes	10 (17.9)	6 (11.5)
No	25 (44.6)	21 (40.4)
Not reported	21 (37.5)[b]	25 (48.1)[b]
Disease status at start of study, n (%)		
Recurrent	8 (14.3)	14 (26.9)
Newly diagnosed	48 (85.7)	38 (73.1)
Prior nephrectomy, n (%)		
Yes	30 (53.6)	31 (59.6)
No	26 (46.4)	21 (40.4)
Treatment discontinuation, n (%)	38 (69.1)[c]	48 (92.3)
Study discontinuation, n (%)	ND	ND

a. Method of analysis unclear.
b. Institute's calculation.
c. Information refers to discontinuation of pembrolizumab + axitinib.

CPS: combined positive score; F: female; M: male; n: number of patients in the category; N: number of randomized patients in the subpopulation with poor risk profile; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The demographic and clinical characteristics are sufficiently balanced between the study arms. The majority of the study participants were male, which is due to the higher disease rate in men [8]. The mean age of the patients was 59 years and most were of white family origin. The majority of the patients in both study arms were in good general condition (Karnofsky performance status of ≥ 90). In the majority of the patients, the disease was newly diagnosed at the start of the study. The number of treatment discontinuations was higher in the sunitinib arm (92%) than in the pembrolizumab + axitinib arm (69%). Information on the reasons for treatment discontinuation is only available for the total population (see Section 2.3.1.2); information on study discontinuation is not available.

Course of the study

Table 19 shows the mean and median treatment duration and the mean and median observation period for individual outcomes.

Table 19: Information on the course of the study – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 2: patients with poor risk profile)

Study **Duration of the study phase** **Outcome category**	**Pembrolizumab + axitinib** **N = 55**	**Sunitinib** **N = 52**
KEYNOTE-426		
Treatment duration [months]		
Median [Q1; Q3]	8.0 [2.0; 17.9]	2.5 [1.7; 6.4]
Mean (SD)	9.9 (8.3)	5.0 (5.3)
Observation period [months]		
Overall survival[a], morbidity, health-related quality of life	ND	ND
Side effects (AEs)		
Median [Q1; Q3]	8.9 [3.0; 18.6]	3.5 [2.5; 7.4]
Mean (SD)	10.4 (7.9)	5.9 (5.3)
Side effects (SAEs)		
Median [Q1; Q3]	9.4 [4.8; 18.6]	5.3 [3.8; 9.2]
Mean (SD)	11.4 (7.4)	7.2 (5.3)

a. For the total study population, the median observation period was 17.2 months in the intervention arm and 15.5 months in the control arm.

AE: adverse event; ASaT: all subjects as treated; N: number of analysed patients in the subpopulation with poor risk profile (ASaT); Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation; vs.: versus

Median treatment duration was 8 months in the pembrolizumab + axitinib arm, which was more than 3 times longer than in the sunitinib arm. Information on observation periods for the outcomes of the categories of “morbidity” and “health-related quality of life” is neither available for the total population nor for the subpopulations. Outcomes on morbidity and health-related quality of life was to be observed until 30 days after treatment discontinuation. It can be

inferred from this that the observation periods for these outcomes were notably longer in the pembrolizumab + axitinib arm than in the sunitinib arm. The median observation period for AEs was 2.5 times (5.4 months) longer in the pembrolizumab + axitinib arm than in the sunitinib arm, and 1.8 times (4.1 months) longer for SAEs.

Risk of bias across outcomes (study level)

Table 11 in Section 2.3.1.2 shows the risk of bias across outcomes (risk of bias at study level).

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The patient-relevant outcomes included in the assessment are presented in Section 2.3.2.1. Table 12 in Section 2.3.2.1 shows for which outcomes data were available in the included KEYNOTE-426 study.

2.4.2.2 Risk of bias

The assessment of the risk of bias of the results for research question 2 corresponds to the assessment for research question 1. Section 2.3.2.2 and Table 13 describe the risk of bias for the results of the relevant outcomes.

2.4.2.3 Results

Table 20 summarizes the results on the comparison of pembrolizumab + axitinib with sunitinib in treatment-naive adult patients with poor risk profile. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The available Kaplan-Meier curves on the event time analyses used are presented in Appendix A, the common AEs in Appendix B of the full dossier assessment.

Table 20: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 2: patients with poor risk profile) (multipage table)

Study Outcome category Outcome	Pembrolizumab + axitinib N	Pembrolizumab + axitinib Median time to event in months[a] [95% CI] Patients with event n (%)	Sunitinib N	Sunitinib Median time to event in months[a] [95% CI] Patients with event n (%)	Pembrolizumab + axitinib vs. sunitinib HR [95% CI]; p-value[b]
KEYNOTE-426					
Mortality					
Overall survival	56	21.8 [14.7; 25.2] 26 (46.4)	52	10.1 [7.0; 17.6] 32 (61.5)	0.50 [0.29; 0.87]; 0.015
Morbidity					
Symptoms (EORTC QLQ-C30 symptom scales)				No usable data[c]	
Symptoms (FKSI-DRS)				No usable data[c]	
Health status (EQ-5D VAS)				No usable data[c]	
Health-related quality of life					
Health-related quality of life (EORTC QLQ-C30 functional scales)				No usable data[c]	
Side effects					
AEs (supplementary information)[d]	*55*	*0.2 [0.1; 0.5]* *52 (94.5)*	*52*	*0.3 [0.2; 0.3]* *52 (100.0)*	–
SAEs[d]	55	9.3 [3.0; NC] 29 (52.7)	52	9.8 [1.9; NC] 25 (48.1)	0.88 [0.51; 1.51]; 0.644
Severe AEs (CTCAE grade ≥ 3)[d]	55	2.7 [1.6; 4.4] 42 (76.4)	52	1.0 [0.6; 2.2] 44 (84.6)	0.60 [0.39; 0.93]; 0.022
Discontinuation due to AEs[d]	55	NA [10.7; NC][e] 15 (27.3)	52	NA 10 (19.2)	1.15 [0.51; 2.59]; 0.728
Immune-related AEs (supplementary information)[f]	*55*	*8.3 [5.5; 12.5]* *24 (43.6)*	*52*	*NA [4.5; NC]* *15 (28.8)*	–
Immune-related SAEs	55	NA 6 (10.9)	52	NA 1 (1.9)	4.08 [0.48; 34.58]; 0.198
Immune-related severe AEs (CTCAE grade ≥ 3)	55	NA [19.5; NC] 6 (10.9)	52	NA 2 (3.8)	1.88 [0.37; 9.56]; 0.448
Nervous system disorders (SOC, AEs)	55	16.9 [8.9; NC] 21 (38.2)	52	3.6 [0.9; NC] 27 (51.9)	0.39 [0.21; 0.72]; 0.003
Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3])	55	NA 2 (3.6)	52	NA [19.7; NC] 11 (21.2)	0.12 [0.03; 0.56]; 0.007
General disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3])	55	NA 3 (5.5)	52	NA 12 (23.1)	0.17 [0.05; 0.62]; 0.007
Metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])	55	NA 7 (12.7)	52	NA [6.0; NC] 16 (30.8)	0.28 [0.11; 0.70]; 0.006

Table 20: Results (mortality, side effects) – RCT, direct comparison: pembrolizumab + axitinib vs. sunitinib (research question 2: patients with poor risk profile) (multipage table)

Study Outcome category Outcome	Pembrolizumab + axitinib N Median time to event in months[a] [95% CI] Patients with event n (%)	Sunitinib N Median time to event in months[a] [95% CI] Patients with event n (%)	Pembrolizumab + axitinib vs. sunitinib HR [95% CI]; p-value[b]
a. Data for side effects: Institute's calculation (weeks in months). b. HR; CI and p-value: Cox proportional hazards model; for the outcome "overall survival" stratified by region (North America vs. Western Europe vs. rest of the world); for the outcomes of the category "side effects" unstratified. c. No usable data available due to unequal documentation times in the study arms; see Section 2.7.4.3.2 of the full dossier assessment for further justification. d. Analysis without the PTs "neoplasm progression", "malignant neoplasm progression" and "disease progression". e. It is not clear from the documents whether this refers to discontinuation of pembrolizumab and/or axitinib. f. In the total population of the study, mainly the PTs "hyperthyroidism" and "hypothyroidism" are included in the outcome at the time point of the first data cut-off. For 30 (about 55%) patients in the intervention arm versus 13 (about 81%) patients in the comparator arm, events based on CTCAE grade 1 were included for hyperthyroidism, and for 49 (32%) vs. 55 (41%) patients for hypothyroidism. CTCAE grade 1 is not patient-relevant for these PTs, as it is defined as "asymptomatic; clinical or diagnostic observations only; intervention not indicated" [9,10]. Information for the second data cut-off is not available. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus		

Based on the available data, no more than indications, e.g. of an added benefit, can be determined. The company derived the added benefit exclusively on the basis of the total study population. For this reason, similarities or deviations in comparison with the assessment of the added benefit by the company are not commented on below.

Mortality

Overall survival

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for the outcome "overall survival". This resulted in an indication of an added benefit of pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Morbidity

Symptoms (recorded with the EORTC QLQ-C30 symptom scales)

There were no usable data for the outcome "symptoms" recorded with the EORTC QLQ-C30 symptom scales (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint

of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Symptoms (recorded with the FKSI-DRS)

There were no usable data for the outcome "symptoms" recorded with the FKSI-DRS (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health status (recorded with the EQ-5D VAS)

There were no usable data for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life (recorded with the EORTC QLQ-C30 functional scales)

There were no usable data for the outcome "health-related quality of life" recorded with the EORTC QLQ-C30 functional scales (see Section 2.7.4.3.2 of the full dossier assessment). Hence, there was no hint of an added benefit of pembrolizumab + axitinib in comparison with sunitinib; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between the treatment arms was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from pembrolizumab + axitinib in comparison with sunitinib; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference between the treatment arms in favour of pembrolizumab + axitinib was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome.

Discontinuation due to AEs

No statistically significant difference between the treatment arms was shown for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from pembrolizumab + axitinib in comparison with sunitinib for this outcome; greater or lesser harm is therefore not proven.

Immune-related SAEs and immune-related severe AEs (CTCAE grade ≥ 3)

No statistically significant difference between the treatment arms was shown for each of the outcomes "immune-related SAEs" and "immune-related severe AEs (CTCAE grade ≥ 3)". This

resulted in no hint of greater or lesser harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes; greater or lesser harm is therefore not proven.

Nervous system disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3]), general disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3]), metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])

A statistically significant difference in favour of pembrolizumab + axitinib was shown between the treatment arms for each of the following outcomes: nervous system disorders, blood and lymphatic system disorders, general disorders and administration site conditions, and metabolism and nutrition disorders. This resulted in a hint of lesser harm from pembrolizumab + axitinib in comparison with sunitinib for each of these outcomes.

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics prespecified in the KEYNOTE-426 study were considered in the benefit assessment:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)
- region (North America versus Western Europe versus rest of the world)

Furthermore, the subgroup characteristic "disease severity according to IMDC score" was investigated in the KEYNOTE-426 study. Since the present assessment was already conducted separately for the patient populations with favourable or intermediate risk profile (research question 1) and with poor risk profile (research question 2) according to IMDC score, this characteristic is not additionally considered.

Interaction tests were performed if at least 10 patients per subgroup were included in the analysis. For binary data, there had to be 10 events in at least one subgroup.

Only results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

For the outcomes of the category "side effects", the dossier contained analyses on subgroup characteristics for the relevant second data cut-off only for the following outcomes: SAEs, discontinuation due to AEs, severe AEs (CTCAE grade ≥ 3), immune-related SAEs and severe immune-related AEs (CTCAE grade ≥ 3).

There were no effect modifications for the outcomes included.

2.4.3 Probability and extent of added benefit

Probability and extent of added benefit for treatment-naive patients with advanced renal cell carcinoma and poor risk profile (research question 2) are derived below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 21).

Determination of the outcome category for the outcomes on side effects

The dossier does not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Nervous system disorders (SOC, AEs)

At the time point of the first data cut-off (24 August 2018), events that had occurred in the specific AE “nervous system disorders” were mostly non-serious. This information refers to the total populations; information for the subpopulation of patients with poor risk profile at the time point of the second data cut-off is not available. The outcome was therefore allocated to the outcome category “non-serious/non-severe side effects”.

Table 21: Extent of added benefit at outcome level: pembrolizumab + axitinib vs. sunitinib (research question 2: patients with poor risk profile) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + axitinib vs. sunitinib** **Median time to event** **HR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	HR: 21.8 vs. 10.1 months 0.50 [0.29; 0.87]; p = 0.015 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms (EORTC QLQ-C30 symptom scales)	No usable data	Lesser benefit/added benefit not proven
Symptoms (FKSI-DRS)	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
Health-related quality of life (EORTC QLQ-C30 functional scales)	No usable data	Lesser benefit/added benefit not proven
Side effects		
SAEs	9.3 vs. 9.8 months HR: 0.88 [0.51; 1.51]; p = 0.644	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	2.7 vs. 1.0 months HR: 0.60 [0.39; 0.93]; p = 0.022 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Discontinuation due to AEs	NA vs. NA HR: 1.15 [0.51; 2.59]; p = 0.728	Greater/lesser harm not proven
Immune-related SAEs	NA vs. NA HR: 4.08 [0.48; 34.58]; p = 0.198	Greater/lesser harm not proven
Immune-related severe AEs (CTCAE grade ≥ 3)	NA vs. NA HR: 1.88 [0.37; 9.56]; p = 0.448	Greater/lesser harm not proven
Nervous system disorders (SOC, AEs)	16.9 vs. 3.6 months HR: 0.39 [0.21; 0.72]; p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ lesser harm, extent: "considerable"
Blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade ≥ 3])	NA vs. NA HR: 0.12 [0.03; 0.56]; p = 0.007 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% lesser harm, extent: "major"

Table 21: Extent of added benefit at outcome level: pembrolizumab + axitinib vs. sunitinib (research question 2: patients with poor risk profile) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Pembrolizumab + axitinib vs. sunitinib** **Median time to event** **HR [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
General disorders and administration site conditions (SOC, severe AEs [CTCAE grade ≥ 3])	NA vs. NA HR: 0.17 [0.05; 0.62]; p = 0.007 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% lesser harm, extent: "major"
Metabolism and nutrition disorders (SOC, severe AEs [CTCAE grade ≥ 3])	NA vs. NA HR: 0.28 [0.11; 0.70]; p = 0.006 probability: "hint"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% lesser harm, extent: "major"

a. Probability provided if a statistically significant and relevant effect is present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life-5 Dimensions; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 22 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 22: Positive and negative effects from the assessment of pembrolizumab + axitinib in comparison with sunitinib (research question 2: patients with poor risk profile)

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of added benefit – extent: "considerable"	-
Serious/severe side effects ▪ Severe AEs (CTCAE grade ≥ 3): hint of lesser harm – extent: "minor", including: ▫ blood and lymphatic system disorders; general disorders and administration site conditions, and metabolism and nutrition disorders: in each case hint of lesser harm – extent: "major"	-
Non-serious/non-severe side effects ▪ Nervous system disorders (AEs): hint of lesser harm – extent: "considerable"	-
There are no usable data for further outcomes on morbidity and health-related quality of life (see Section 2.7.4.3.2 of the full dossier assessment).	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

Overall, only positive effects with different probability and extent were shown for pembrolizumab + axitinib in comparison with sunitinib. The indication of considerable added benefit of pembrolizumab + axitinib for the outcome "overall survival" was decisive for the overall conclusion on the added benefit. This was supported by the positive effects in the outcome category of side effects.

In summary, there is an indication of considerable added benefit of pembrolizumab + axitinib versus the ACT for treatment-naive adult patients with advanced renal cell carcinoma with poor risk profile.

The assessment described above deviates from that of the company, which derived an indication of a major added benefit for the total patient population in the therapeutic indication regardless of the risk profile. The company did not provide separate information on the added benefit for the relevant subpopulation of patients with poor risk profile (research question 2 of the present benefit assessment) (see Section 2.7.2 of the full dossier assessment).

2.5 Probability and extent of added benefit – Summary

The result of the assessment of the added benefit of pembrolizumab + axitinib in comparison with the ACT is summarized in Table 23.

Table 23: Pembrolizumab + axitinib – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adult patients with advanced renal cell carcinoma with favourable or intermediate risk profile (0–2 risk factors of the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or monotherapy with **sunitinib**	Indication of considerable added benefit[b]
2	Treatment-naive adult patients with advanced renal cell carcinoma with poor risk profile (≥ 3 risk factors of the IMDC criteria)	Temsirolimus or **sunitinib**	Indication of considerable added benefit[b]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The KEYNOTE-426 study did not investigate patients with non-clear cell renal cell carcinoma or with Karnofsky performance status < 70%. It remains unclear whether the observed effects can be transferred to these patients.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

Merck Sharp & Dohme. Study to evaluate the efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy in participants with renal cell carcinoma (MK-3475-426/KEYNOTE-426): study details [online]. In: ClinicalTrials.gov. 10.12.2019 [Accessed: 12.12.2019]. URL: https://ClinicalTrials.gov/show/NCT02853331.

Merck Sharp & Dohme. Eine randomisierte, offene Phase III Studie zur Beurteilung der Wirksamkeit und Sicherheit von Pembrolizumab (MK-3475) in Kombination mit Axitinib im Vergleich zu einer Monotherapie mit Sunitinib als Erstlinienbehandlung bei lokal fortgeschrittenem oder metastasiertem Nierenzellkarzinom (mRCC) (KEYNOTE-426) [online]. In: Deutsches Register Klinischer Studien. [Accessed: 12.12.2019]. URL: http://www.drks.de/DRKS00011432.

Merck Sharp & Dohme. Study to evaluate the efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy in participants with renal cell carcinoma (MK-3475-426/KEYNOTE-426): study results [online]. In: ClinicalTrials.gov. 10.12.2019 [Accessed: 12.12.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02853331.

Merck Sharp & Dohme. A phase III randomized, open-label study to evaluate efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or metastatic renal cell carcinoma (mRCC) (KEYNOTE-426) [online]. In: EU Clinical Trials Register. [Accessed: 12.12.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000588-17.

Merck Sharp & Dohme. A phase III randomized, open-label study to evaluate efficacy and safety of pembrolizumab (MK-3475) in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or metastatic renal cell carcinoma (mRCC) (KEYNOTE-426): study P426V01MK3475; clinical study report [unpublished]. 2018.

Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019; 380(12): 1116-1127.

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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