IQWiG Reports – Commission No. A19-11

Nivolumab (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 *Nivolumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 May 2019). 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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Table of contents

List of tables[2]

Page

[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
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
FACT-G	Functional Assessment of Cancer Therapy-General
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	intravenously
IVRS	interactive voice response system
MD	mean difference
MMRM	mixed-effects model repeated measures
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
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 nivolumab. 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 4 February 2019.

Research question

The aim of the present report was to assess the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in comparison with the appropriate comparator therapy (ACT) in treatment-naive adult patients with intermediate or poor-risk advanced renal cell carcinoma.

Table 2 shows the research questions of the benefit assessment and the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of nivolumab + ipilimumab

Research question	**Subindication**	**ACT[a]**
1	Treatment-naive adult patients with intermediate-risk advanced renal cell carcinoma (1−2 risk factors as per the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or **sunitinib**
2	Treatment-naive adult patients with poor-risk advanced renal cell carcinoma (≥ 3 risk factors as per 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 for both research questions from the options presented. Deviating from the G-BA, the company considered patients with intermediate and poor risk profile together as one patient population. 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 for research questions 1 and 2

The study pool for the present benefit assessment of nivolumab + ipilimumab in comparison with the ACT consisted of the RCT CheckMate 214.

The CheckMate 214 study was a randomized, open-label, active-controlled approval study on the comparison of nivolumab + ipilimumab with sunitinib. The study included adults with previously untreated advanced clear-cell renal cell carcinoma in stage IV according to the American Joint Committee on Cancer (AJCC). The patients had to be in good general condition (Karnofsky performance status of ≥ 70%). Patients with non-clear cell renal cell carcinoma and active brain metastases were excluded from study participation.

Patients were included in the study irrespective of their risk profile. However, criteria were formulated in the study to allow distinguishing patients with intermediate/poor risk (= target population of the present benefit assessment) from those with favourable risk. According to these criteria, the risk profile of patients with ≥ 1 of the following prognostic factors of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score was considered intermediate/poor.

- Karnofsky performance status = 70%
- < 1 year between diagnosis and randomization
- haemoglobin below normal
- calcium (corrected value) above lower normal value
- absolute neutrophil count above normal
- absolute platelet count above normal

If none of the factors were present, the risk profile of the patients was considered favourable.

A total of 550 patients were randomly allocated to the nivolumab + ipilimumab arm, and 546 patients to the sunitinib arm of the study. Randomization was stratified by region (USA versus Canada, Western Europe, Northern Europe versus rest of the world) and baseline IMDC score (information from the interactive voice response system [IVRS]: favourable versus intermediate versus poor, defined as 0 versus 1 to 2 versus 3 to 6 risk factors of the IMDC score).

In the 12-week induction phase, patients in the intervention group of the study received nivolumab 3 mg/kg body weight (intravenously [IV] over 60 minutes) in combination with ipilimumab 1 mg/kg body weight (IV over 30 minutes) every 3 weeks. In the maintenance phase, nivolumab 3 mg/kg body weight (IV over 60 minutes) was administered every 2 weeks. The comparator group received daily sunitinib 50 mg orally. 4 weeks of continuous administration of sunitinib were followed by a 2-week rest period.

The dosing regimen of nivolumab monotherapy used in the maintenance phase of the CheckMate 214 approval study deviated from the dosage described in the Summary of Product Characteristics (SPC). The SPC prescribes a dose of 240 mg every 2 weeks or 480 mg every 4 weeks regardless of body weight for the maintenance phase of nivolumab monotherapy. Furthermore, the SPC recommends an infusion time of 30 minutes both for the body-weight-dependant dosage in the induction phase and for the nivolumab monotherapy dose of 240 mg in the maintenance phase. For the comparison examined in the present benefit assessment, however, it was assumed that the deviation in the dosage regimen of nivolumab had no relevant influence on the observed effects.

The CheckMate 214 study was ended prematurely following the first interim analysis (7 August 2017). The present benefit assessment was based on the second planned interim analysis of the CheckMate 214 study from 6 August 2018. The final analysis of the CheckMate 214 study is planned after 639 deaths and is still pending.

Results for research question 1: patients with intermediate-risk advanced renal cell carcinoma

The subpopulation of patients from the CheckMate 214 study with 1 to 2 IMDC risk factors was considered for research question 1 of the present benefit assessment (patient population with intermediate risk).

Risk of bias

The risk of bias at study level was rated as low. The risk of bias at outcome level was rated as high for all outcomes except overall survival.

Results

Mortality

A statistically significant difference in favour of nivolumab + ipilimumab was shown between the treatment arms for the outcome “overall survival”. This resulted in an indication of an added benefit of nivolumab + ipilimumab in comparison with sunitinib for the outcome “overall survival”.

Morbidity

A statistically significant result in favour of nivolumab + ipilimumab was shown for the outcome “symptoms” (recorded using the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]). The standardized mean difference (SMD) in the form of Hedges’ g was considered to check the relevance of the statistically significant results. The 95% confidence interval (CI) of the SMD was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. Under consideration of the risk of bias, this resulted in a hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib for the outcome “symptoms” (FKSI-DRS).

A statistically significant difference between the treatment arms in favour of nivolumab + ipilimumab was shown for health status (recorded using the European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS] questionnaire). However, the 95% CI of the SMD (Hedges' g) was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

A statistically significant difference in favour of nivolumab + ipilimumab was shown for the outcome "health-related quality of life" (recorded using the Functional Assessment of Cancer Therapy-General [FACT-G]) for the total score. The 95% CI of the SMD (Hedges' g) was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. Under consideration of the risk of bias, this resulted in a hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib for the outcome "health-related quality of life" (FACT-G).

Results on side effects

Based on the methodology for selecting specific AEs, a high number of specific AEs were included in the present assessment. As a result, the results of the side effect outcomes are interpreted together below and considered in the balancing of positive and negative effects.

Regarding side effect outcomes, there were both advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib.

There were statistically significant differences between the treatment arms in favour of nivolumab + ipilimumab in comparison with sunitinib in the following AEs:

- specific AEs (AEs, serious AEs [SAEs], severe AEs [Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4]):
  - malaise (Preferred Term [PT], AE)
  - mucosal inflammation (PT, severe AE [CTCAE grade 3–4])
  - gastrointestinal disorders (System Organ Class [SOC], AE)
  - hair colour changes (PT, AE)
  - yellow skin (PT, AE)
  - oedema (PT, AE)
  - epistaxis (PT, AE)
  - dysgeusia (PT, AE)
  - palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])

- hypertension (PT, severe AE [CTCAE grade 3–4])
- blood and lymphatic system disorders (PT, severe AE [CTCAE grade 3–4])

Significant differences between the treatment arms to the disadvantage of nivolumab + ipilimumab in comparison with sunitinib were shown for

- SAEs
- discontinuation due to AEs
- specific AEs (AEs, SAEs, severe AEs [CTCAE grade 3–4])
  - influenza like illness (PT, AE)
  - rash (PT, AE)
  - arthralgia (PT, AE)
  - diarrhoea (PT, SAE)
  - pruritus (PT, AE)
  - myalgia (PT, AE)
  - pneumonia (PT, severe AE [CTCAE grade 3–4])
  - pneumonitis (PT, SAE)
  - hyperglycaemia (PT, severe AE [CTCAE grade 3–4])
  - endocrine disorders (SOC, severe AE [CTCAE grade 3–4])

No statistically significant difference between the treatment arms was shown for the outcome "severe AEs" (CTCAE grade 3–4). There were no usable data for the outcome "immune-related AEs".

Overall, there were hints both of lesser and of greater harm from nivolumab + ipilimumab in comparison with sunitinib with the extents "minor" to "major". Indications of lesser or greater harm were derived for individual specific AEs. In the overall consideration, the advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib regarding side effects were balanced. Overall, this resulted in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with sunitinib for side effects; greater or lesser harm is therefore not proven.

Results for research question 2: patients with poor-risk advanced renal cell carcinoma

The subpopulation of patients from the CheckMate 214 study with 3 to 6 IMDC risk factors was considered for research question 2 of the present benefit assessment (patient population with poor risk).

Risk of bias

The risk of bias at study level was rated as low. The risk of bias at outcome level was rated as high for all outcomes except overall survival.

Results

Mortality

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

Morbidity

There was no statistically significant difference between the treatment arms for the outcomes "symptoms""(FKSI-DRS) and "health status" (EQ-5D VAS). In each case, this resulted in no hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

No statistically significant difference between the treatment arms was shown for the outcome "health-related quality of life" (FACT-G). This resulted in no hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib; an added benefit is therefore not proven.

Side effects

- Serious adverse events, severe adverse events (CTCAE grade 3–4) and discontinuation due to adverse events

No statistically significant difference between the treatment arms was shown for the outcomes "SAEs", "severe AEs" (CTCAE grade 3–4) and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with sunitinib; greater or lesser harm is therefore not proven.

- Specific adverse events

Significant differences between the treatment arms in favour of nivolumab + ipilimumab in comparison with sunitinib were shown for the following outcomes: stomatitis, mucosal inflammation, epistaxis, palmar-plantar erythrodysaesthesia syndrome, dysgeusia, respiratory, thoracic and mediastinal disorders, hypothyroidism, gastrointestinal disorders, and thrombocytopenia. Under consideration of the risk of bias, this resulted in a hint of lesser harm of nivolumab + ipilimumab in comparison with sunitinib for individual outcomes.

There were statistically significant differences between the treatment arms to the disadvantage of nivolumab + ipilimumab in comparison with sunitinib for the outcomes "fever", "pruritus" and "ear and labyrinth disorders". Under consideration of the risk of bias, this resulted in a hint

of greater harm of nivolumab + ipilimumab in comparison with sunitinib for individual outcomes.

- Immune-related adverse events

There were no usable data for the outcome "immune-related AEs".

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

On the basis of the results presented, the probability and extent of the added benefit of the drug nivolumab + ipilimumab compared with the ACT is assessed as follows:

Research question 1: patients with intermediate-risk advanced renal cell carcinoma

On the positive side, there was an indication of considerable added benefit of nivolumab + ipilimumab for the outcome "overall survival" and a hint of a non-quantifiable added benefit for the outcomes "health-related quality of life" (FACT-G) and "symptoms" (FKSI-DRS).

Regarding side effects, the advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib were balanced, so that overall there is no hint of greater or lesser harm from nivolumab + ipilimumab compared with the ACT.

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

Research question 2: patients with poor-risk advanced renal cell carcinoma

In the overall assessment, there are both positive and negative effects with different certainty of results (indication or hint) for nivolumab + ipilimumab in comparison with sunitinib in patients with poor-risk advanced renal cell carcinoma.

An indication of a major added benefit was shown for the outcome "overall survival". Furthermore, hints of lesser harm with different extents were shown for a number of outcomes of the category of side effects with different severity grades.

On the negative side, there were hints of greater harm with different extents of nivolumab + ipilimumab versus sunitinib for 3 outcomes of the category of side effects.

[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 major added benefit of nivolumab + ipilimumab versus the ACT for treatment-naive adult patients with poor-risk advanced renal cell carcinoma.

Table 3 presents a summary of the probability and extent of the added benefit of nivolumab + ipilimumab.

Table 3: Nivolumab + ipilimumab – probability and extent of added benefit

Research question	**Subindication**	**ACT**[a]	**Probability and extent of added benefit**
1	Treatment-naive adult patients with intermediate-risk advanced renal cell carcinoma (1−2 risk factors as per the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or **sunitinib**	Indication of considerable added benefit[b]
2	Treatment-naive adult patients with poor-risk advanced renal cell carcinoma (≥ 3 risk factors as per the IMDC criteria)	Temsirolimus or **sunitinib**	Indication of a major 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 CheckMate 214 study underlying the benefit assessment did not investigate patients with non-clear cell renal cell carcinoma, advanced AJCC stage III renal cell carcinoma, brain metastases, or Karnofsky performance status < 70% (see Section 2.7.4.1 of the full dossier assessment). It is unclear whether the observed effects are transferable to patients with the characteristics described above.
ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; 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 was to assess the added benefit of nivolumab in combination with ipilimumab (hereinafter referred to as "nivolumab + ipilimumab") in comparison with the ACT in treatment-naive adult patients with intermediate or poor-risk advanced renal cell carcinoma.

Table 4 shows the research questions of the benefit assessment and the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of nivolumab + ipilimumab

Research question	Subindication	ACT[a]
1	Treatment-naive adult patients with intermediate-risk advanced renal cell carcinoma (1−2 risk factors as per the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or **sunitinib**
2	Treatment-naive adult patients with poor-risk advanced renal cell carcinoma (≥ 3 risk factors as per 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 for both research questions from the options presented. Deviating from the G-BA, the company considered patients with intermediate and poor risk profile together as one patient population (see Section 2.7.1 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 intermediate risk

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 nivolumab + ipilimumab (status: 13 November 2018)
- bibliographical literature search on nivolumab + ipilimumab (last search on 6 November 2018)
- search in trial registries for studies on nivolumab + ipilimumab (last search on 13 November 2018)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab + ipilimumab (last search on 12 February 2019)

The check identified no additional relevant study.

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: nivolumab + ipilimumab 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)
CA209-214 (CheckMate 214[b])	Yes	Yes	No

a: Study sponsored by the company.
b: In the following tables, the study is referred to with this designation.
RCT: randomized controlled trial; vs.: versus

The study pool for the present benefit assessment of nivolumab + ipilimumab in comparison with the ACT consisted of the RCT CheckMate 214 and corresponded to the study pool of the company.

Besides patients with intermediate or poor risk, the CheckMate 214 study also included patients with favourable risk.

The company used the results of the subpopulation of patients with intermediate or poor risk as joint patient population for its assessment and derived the added benefit exclusively for this joint patient population. The company did not provide separate information on the added benefit for the respective relevant subpopulations of research questions 1 and 2 of the present benefit assessment.

The present benefit assessment used the results of the patient population with intermediate risk for research question 1 and the results of the patient population with poor risk for research question 2. The added benefit of nivolumab + ipilimumab was derived separately for both patient populations. This was possible because, in Module 4 J, the company also presented separate analyses for the patient populations of research questions 1 and 2 of the present benefit assessment in addition to the analyses of a joint consideration of both populations primarily used by the company.

Section 2.6 contains a reference list for the study included.

2.3.1.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CheckMate 214	RCT, open-label, parallel	Treatment-naive adult patients with advanced or metastatic clear-cell renal cell carcinoma (AJCC stage IV)	Nivolumab + ipilimumab (N = 550) sunitinib (N = 546) Relevant subpopulations thereof: ▪ patients with intermediate risk: nivolumab + ipilimumab (n = 334) sunitinib (n = 333) ▪ Patients with poor risk: nivolumab + ipilimumab (n = 91) sunitinib (n = 89)	Screening: 28 days Treatment: until disease progression[b], unacceptable toxicity or treatment discontinuation following the physician's or patient's decision Observation[c]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	174 centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Columbia, Chile, Czech Republic, Denmark, Finland, France, Germany, Great Britain, Hungary, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Poland, South Korea, Spain, Sweden, Taiwan, Turkey, USA 10/2014–ongoing[d] <u>Data cut-offs:</u> ▪ 11 Oct 2016: ORR analysis ▪ 7 Aug 2017: interim analysis of overall survival and final analysis of ORR and PFS ▪ 1 Mar 2018: Analysis of overall survival[e] ▪ 6 Aug 2018: interim analysis of overall survival	Primary: overall survival, PFS, ORR 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: All patients could continue their respective study treatment also after initial progression if there was a clinical benefit and treatment was tolerated. After further disease progression, treatment was to be discontinued.
c: Outcome-specific information is provided in Table 8.
d: The study was ended prematurely based on the first interim analysis (August 2017); the follow-up observation phase is ongoing.
e: Analysis conducted at the request of the regulatory authority.

AE: adverse event; AJCC: American Joint Committee on Cancer; n: relevant subpopulation; N: number of randomized patients; ORR: objective response rate; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

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

Study	Intervention	Comparison
CheckMate 214	Induction phase: nivolumab 3 mg/kg body weight IV + ipilimumab 1 mg/kg body weight IV every 3 weeks for 4 cycles Then maintenance phase: nivolumab 3 mg/kg body weight IV, every 2 weeks[a] Dose adjustments: ▪ no dose adjustments allowed ▪ dose delays due to AEs allowed	Sunitinib 50 mg orally daily, continuous cycles: 4 weeks of administration, 2-week rest period Dose adjustments: ▪ dose reduction at most 2x in 12.5 mg steps up to ≥ 25 mg daily ▪ dose escalation in compliance with the SPC allowed ▪ dose delays due to AEs allowed
	<u>Permitted pretreatment:</u> ▪ 1 adjuvant or neoadjuvant therapy for completely resectable renal cell carcinoma (if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy) **<u>Non-permitted pretreatment:</u>** ▪ systemic VEGF or VEGF receptor targeted therapy ▪ treatment with antibodies (e.g. against PD-1, PD-L1, PD-L2) or other T-cell co-stimulators ▪ systemic corticosteroids > 10 mg/day ▪ immunosuppressive medications within 14 days before baseline ▪ major surgery < 28 days before baseline ▪ anticancer therapy < 28 days before baseline ▪ palliative local radiotherapy < 14 days before baseline **<u>Permitted concomitant treatment:</u>** ▪ inhaled, topical, ocular, intraarticular, intranasal corticosteroids with minimal systemic absorption ▪ adrenal replacement steroids > 10 mg/day **Non-permitted concomitant treatment** ▪ immunosuppressants (except for the treatment of AEs) ▪ other antineoplastic treatment	

a: Following Amendment 14 (October 2017), the patients could be switched to the maintenance phase nivolumab dose regardless of body weight of 240 mg every 2 weeks.

AE: adverse event; IV: intravenously; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; VEGF: vascular endothelial growth factor; vs.: versus

Study design

Patient population

The CheckMate 214 study was a randomized, open-label, active-controlled approval study on the comparison of nivolumab + ipilimumab with sunitinib. The study included adults with previously untreated advanced AJCC stage IV clear-cell renal cell carcinoma. The patients had to be in good general condition (Karnofsky performance status of ≥ 70%). Patients with non-clear cell renal cell carcinoma and active brain metastases were excluded from study participation.

Patients were included in the study irrespective of their risk profile. However, criteria were formulated in the study to allow distinguishing patients with intermediate/poor risk (= target population of the present benefit assessment) from those with favourable risk. According to these criteria, the risk profile of patients with ≥ 1 of the following prognostic factors of the IMDC score was considered intermediate/poor.

- Karnofsky performance status = 70%
- < 1 year between diagnosis and randomization
- haemoglobin below normal
- calcium (corrected value) above lower normal value
- absolute neutrophil count above normal
- absolute platelet count above normal

If none of the factors were present, the risk profile of the patients was considered favourable.

A total of 550 patients were randomly allocated to the nivolumab + ipilimumab arm, and 546 patients to the sunitinib arm of the study. Randomization was stratified by region (USA versus Canada, Western Europe, Northern Europe versus rest of the world) and baseline IMDC score (information from the IVRS: favourable versus intermediate versus poor, defined as presence of 0 versus 1 to 2 versus 3 to 6 risk factors of the IMDC score).

Patient population of the CheckMate 214 study considered by the company

In Module 4 J, the company considered the patient population with intermediate risk (1 to 2 risk factors according to the IMDC) or poor risk (3 to 6 risk factors according to the IMDC) as a joint patient population. In accordance with the G-BA's specification of the ACT, however, the patient populations with intermediate and poor risk were considered as separate subpopulations for research questions 1 and 2 of the present benefit assessment.

Interventions

Treatment of the patients in both study arms was conducted according to the regimen described in Table 7 of the present benefit assessment. In the 12-week induction phase, patients in the intervention group of the study received nivolumab 3 mg/kg body weight (IV over 60 minutes)

in combination with ipilimumab 1 mg/kg body weight (IV over 30 minutes) every 3 weeks. In the maintenance phase, nivolumab 3 mg/kg body weight (IV over 60 minutes) was administered every 2 weeks. The comparator group received daily sunitinib 50 mg orally. 4 weeks of continuous administration of sunitinib was followed by a 2-week rest period.

The dosing regimen of nivolumab monotherapy used in the maintenance phase of the CheckMate 214 approval study deviated from the dosage described in the SPC. The SPC prescribes a dose of 240 mg every 2 weeks or 480 mg every 4 weeks regardless of body weight for the maintenance phase of nivolumab monotherapy [3,4]. Furthermore, the SPC recommends an infusion time of 30 minutes both for the body-weight-dependant dosage in the induction phase and for the nivolumab monotherapy dose of 240 mg in the maintenance phase.

According to its own statements, the company had applied to the European Medicines Agency (EMA) for a change in the approved dosage of nivolumab in parallel with the procedure for extending the therapeutic indication for nivolumab + ipilimumab for the first-line treatment of advanced renal cell carcinoma. The company's application was mainly based on modelling of pharmacokinetic and clinical data on selected outcomes [5]. According to the EMA assessment, the 2 dosing regimens (regardless of body weight and depending on body weight) are comparable in the present therapeutic indication regarding efficacy and safety. The company did not present any studies of direct comparisons between old and new dosing regimen that investigate the effects on patient-relevant outcomes. For the comparison examined in the present benefit assessment, however, it was assumed that the deviation in the dosage regimen of nivolumab had no relevant influence on the observed effects.

Patients were treated until progression or unacceptable persistent toxicity. Under certain conditions, patients could continue treatment beyond disease progression at the investigator's discretion.

Subsequent therapies

There were no limitations regarding subsequent therapy after progression. In the subpopulation of patients with intermediate risk, 48.2% of the patients in the nivolumab + ipilimumab arm received subsequent systemic therapy. The most common subsequent therapies used were sunitinib (23.7%), axitinib (17.1%) and pazopanib (15.9%). In the sunitinib arm, 64% of the patients received subsequent systemic therapy, with nivolumab (36%), axitinib (22.5%) and everolimus (10.8%) being the most common subsequent therapies.

In the subpopulation of patients with poor risk, 44% of the patients in the nivolumab + ipilimumab arm received subsequent systemic therapy. The most common subsequent therapies used were pazopanib (19.8%), sunitinib (16.5%) and axitinib (12.1%). In the sunitinib arm, 49.4% of the patients received subsequent systemic therapy, with nivolumab (25.8%), axitinib (19.1%) and everolimus (11.2%) being the most common subsequent therapies.

Treatment switching

Switching to the treatment of the respective other study arm was not allowed in the course of the study. Only after the premature end of study following the first interim analysis (7 August 2017), Amendment 14 (13 November 2017) allowed patients in the sunitinib arm who were no longer receiving sunitinib, to be switched to nivolumab + ipilimumab in the follow-up observation period. The present benefit assessment was based on the second planned interim analysis of the CheckMate 214 study from 6 August 2018. Hence, the data on the present data cut-off included about 3 years of study duration before and about 10 months of study duration after the allowed treatment switching. The company did not present any information on the number of patients switching from the sunitinib arm to the intervention arm. It was assumed in the present data situation, however, that the treatment switch had no decisive effects on the results on relevant outcomes (see Section 2.7.4.2 of the full dossier assessment).

The final analysis of the CheckMate 214 study is planned after 639 deaths and is still pending.

Outcomes

Primary outcomes of the study were progression-free survival, objective response rate and overall survival. Secondary outcomes were symptoms, health-related quality of life and side effects.

Planned duration of follow-up

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: nivolumab + ipilimumab versus sunitinib

Study **Outcome category** **Outcome**	**Planned follow-up observation**
CheckMate 214	
Mortality	
Overall survival	First follow-up visit[a] and second follow-up visit[b], then every 3 months until death, end of study or withdrawal of consent to be contacted[c]
Morbidity	
Symptoms (FKSI-DRS)	First follow-up visit[a] and second follow-up visit[b]
Health status (EQ-5D VAS)	First follow-up visit[a] and second follow-up visit[b], then every 3 months for 1 year, then every 6 months until death, discontinuation of participation in the study, or lost to follow-up
Health-related quality of life	
FACT-G	First follow-up visit[a] and second follow-up visit[b]
All outcomes in the category "side effects"	Follow-up observation period of 100 days (30 days for discontinuation due to AEs) after the last dose of study medication[d]

a: 30 ± 7 days after the last dose of the study medication or on the day of study discontinuation ± 7 days if this was ≥ 37 days after the last dose.
b: 84 ± 7 days after the first follow-up visit.
c: At most 5 years after the primary analysis of overall survival.
d: Later toxicities were documented also beyond the follow-up observation period of 100 (or 30) days.
AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

In the CheckMate 214 study, the planned follow-up observation of the patients for the outcome "overall survival" was conducted until death, discontinuation of participation in the study or end of study. The study is currently in the follow-up phase, which can last until at most 5 years after the final analysis of overall survival. The CheckMate 214 study is expected to end in December 2019.

Follow-up observation on the outcome categories of morbidity and health-related quality of life (recorded using the FKSI-DRS and the FACT-G) was conducted in 2 follow-up visits. The first follow-up visit was planned for 30 ± 7 days after discontinuation of treatment. The second follow-up visit was planned for 84 ± 7 days after the first one.

Health status measured with the EQ-5D VAS was to be recorded at the first and second follow-up visit, then every 3 months for 1 year, and then every 6 months until death, discontinuation of participation in the study or end of study.

Follow-up observation on side effects was for 100 days (30 days for discontinuation due to AEs) after the last dose of study medication. Toxicities in the study were documented also beyond the follow-up observation period of 100 (or 30) days. These events were not included

in the analysis of the results on AEs, however. In addition, it was not clear from the study documents whether this documentation was systematic.

The observation periods for the outcomes “symptoms” and “health-related quality of life” were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus first and second follow-up visits). The analyses on side effects were also based on systematically shorter observation periods as only data on the follow-up observation period of 100 (or 30) days were included in these analyses, although side effects were recorded beyond this period. 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 and analyse these outcomes over the total period of time, as was the case for survival and health status.

Patient characteristics

Table 9 shows the characteristics of the patients with intermediate risk in the included study.

Table 9: Characteristics of the study population – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate prognosis)

Study Characteristics Category	**Nivolumab + ipilimumab**	**Sunitinib**
CheckMate 214	N = 334	N = 333
Age [years], mean (SD)	61 (10)	60 (10)
Sex [F/M], %	26/74	27/73
Ethnicity, n (%)		
White	290 (86.8)	290 (87.1)
Black or African American	5 (1.5)	4 (1.2)
Asian	30 (9.0)	33 (9.9)
Other	9 (2.7)	6 (1.8)
Region		
USA	86 (25.7)	85 (25.5)
Canada, Western Europe, Northern Europe	119 (35.6)	118 (35.4)
Rest of the world	129 (38.6)	130 (39.0)
Karnofsky performance status, n (%)		
100	150 (44.9)	142 (42.6)
90	103 (30.8)	109 (32.7)
80	50 (15.0)	55 (16.5)
70	31 (9.3)	27 (8.1)
< 70	0 (0)	0 (0)
Time between first diagnosis and randomization [years], n (%)		
< 1	214 (64.1)	219 (65.8)
≥ 1	120 (35.9)	114 (34.2)
Prior nephrectomy, n (%)		
Yes	284 (85.0)	262 (78.7)
No	50 (15.0)	71 (21.3)
PD-L1 status[a], n (%)		
Positive (≥ 5% tumour cell membrane staining)	43 (12.9)[b]	56 (16.8)[b]
Negative (< 5% tumour cell membrane staining)	261 (78.1)[b]	254 (76.3)[b]
Not reported	30 (9.0)	23 (6.9)
Treatment discontinuation, n (%)[c]	ND	ND
Study discontinuation, n (%)	ND	ND

a: Determined using the Dako PD-L1 IHC 28-8 pharmDx test.
b: Information based on Institute's calculation.
c: No information available for the subpopulation of patients with intermediate risk. In the total population of the study, which also includes patients with favourable risk, 76.2% of the patients in the nivolumab + ipilimumab arm and 80.2% in the sunitinib arm discontinued treatment. The most common reasons for treatment discontinuation were disease progression and unacceptable toxicity.

F: female; M: male; n: number of patients in the category; N: number of randomized patients; 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 in the subpopulation with intermediate risk were sufficiently balanced between the study arms. Most patients were male, had a mean age of about 61 years and were of Caucasian origin. The majority of the patients in both study arms were in good general condition (Karnofsky performance status of ≥ 80). There was no information on treatment or study discontinuation.

Course of the study

Table 10 shows the median treatment duration of the patients with intermediate risk and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: (research question 1: patients with intermediate prognosis)

Study **Duration of the study phase** **Outcome category**	**Nivolumab + ipilimumab**	**Sunitinib**
CheckMate 214	N = 333[a]	N = 329[a]
Treatment duration [months]		
Median[b] [min; max]	7.85 [0.0; 41.2]	6.70 [0.0; 39.1]
Observation period [months]		
Overall survival[c]		
Median [min; max]	32.72 [0.0; 43.2]	29.37 [0.6; 43.2]
Morbidity, health-related quality of life, side effects		
Median [min; max]	ND	ND

a: Information provided by the company on treatment durations and observation periods is based on the safety population.
b: Kaplan-Meier estimation; treatment durations of patients who were still receiving the study medication at the date of analysis were censored.
c: The company provides no information as to what this observation period refers to. It is assumed that this is the observation period for the outcome "overall survival".
max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The median treatment duration and the median observation period for the outcome "overall survival" were sufficiently similar between the treatment groups for patients with intermediate prognosis.

The dossier contained no information on observation periods of other outcomes. It can be assumed that observation periods are also comparable between both treatment groups in outcomes with time points of observations that are linked to treatment duration.

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: nivolumab + ipilimumab 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			
CheckMate 214	Yes	Yes	No	No	Unclear[a]	Yes	Low
a: Interim analyses based on smaller sample size than planned. RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low. 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 (FKSI-DRS)
  - health status measured with the VAS of the EQ-5D
- Health-related quality of life
  - health-related quality of life (FACT-G)
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3–4)
  - discontinuation due to AEs
  - immune-related AEs
  - if applicable, further specific AEs

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

Table 12 shows for which outcomes data were available in the included CheckMate 214 study.

Table 12: Matrix of outcomes – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib

Study	Outcomes								
	Overall survival	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-G)	SAEs[a]	Discontinuation due to AEs[a]	Severe AEs (CTCAE grade ≥ 3)[a]	Immune-related AEs	Further specific AEs[b]
CheckMate 214	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes

a: Analysis without recording of progression of the underlying disease and 100 days of follow-up after the end of treatment (discontinuation due to AEs: 30 days of follow-up).
b: Analysis on 30 days follow-up observation after end of treatment.
c: No usable data available; for reasons, see Section 2.7.4.3.2 of the full dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; RCT: randomized controlled trial; SAE: serious adverse event; 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: nivolumab + ipilimumab vs. sunitinib

Study	Study level	Outcomes								
		Overall survival	Symptoms (FKSI-DRS)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-G)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Immune-related AEs	Further specific AEs
CheckMate 214	L	L	H[a, b]	H[a, b, c]	H[a, b]	H[d]	H[a, d]	H[d, e]	-[f]	H[a, d, e]

a: Lack of blinding in subjective recording of outcomes.
b: Unclear proportion of missing values not explicable by death.
c: Possibility for patients in the control arm to switch treatment to nivolumab + ipilimumab in the course of the study.
d: Incomplete observations for potentially informative reasons; no information on reasons for discontinuation.
e: Due to differences in median treatment durations (and resulting observation periods); patients with intermediate prognosis (7.9 months vs. 6.7 months) or with poor risk (5.1 months vs. 3.6 months).
f: No usable data available; for reasons, see Section 2.7.4.3 of the full dossier assessment.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

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

Due to the lack of blinding in subjective recording of outcomes and decreasing response to questionnaires in the course of the study, which cannot be explained by death alone, the risk of bias was rated as high for the results of the outcomes "symptoms" (FKSI-DRS), "health status" (EQ-5D VAS) and "health-related quality of life" (FACT-G). The assessment of a high risk of bias concurs with that of the company. In the outcome "health status" (EQ-5D VAS), the possibility for patients in the control arm to switch treatment to nivolumab + ipilimumab was taken into account in the assessment of the risk of bias of the results.

Due to potentially informative censoring, the risk of bias for results of the outcomes "SAEs", "discontinuation due to AEs" and "severe AEs" (CTCAE grade 3–4) was rated as high. For the outcome "discontinuation due to AEs", with lack of blinding, there was additionally subjective recording of outcomes. The different observation periods constituted an aspect of bias in the

results of the outcome “severe AEs” (CTCAE grade 3–4) (see Section 2.7.4.2 of the full dossier assessment). The assessment of a high risk of bias concurs with that of the company.

Since the company only presented naive rates, the Institute conducted its own calculations for the included outcomes of specific AEs. The risk of bias for the results of this outcome was therefore assessed subsequently (see Section 2.7.4.2 of the full dossier assessment). The risk of bias was rated as high due to the longer treatment duration and the resulting longer observation period in the nivolumab + ipilimumab arm, potentially informative censoring and lack of blinding in subjective recording of outcomes.

2.3.2.3 Results

Table 14, Table 15 and Table 16 summarize the results on the comparison of nivolumab + ipilimumab in treatment-naive adult patients with intermediate-risk advanced renal cell carcinoma. 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 outcomes included 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: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate risk)

Study Outcome category	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
Outcome	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**N**	**Median time to event in months [95% CI] Patients with event n (%)**	**HR [95% CI]; p-value[a]**
CheckMate 214					
Mortality					
Overall survival	334	NA 124 (37.1)	333	34.83 [28.62; NC] 159 (47.7)	0.70 [0.55; 0.88]; 0.003
Side effects					
AEs (additional information)[b]	333	0.26 [0.23; 0.33] 329 (98.8)	329	0.26 [0.20; 0.30] 325 (98.8)	–
SAEs[b]	333	9.13 [5.88; 12.29] 192 (57.7)	329	20.83 [14.95; 31.01] 145 (44.1)	1.38 [1.11; 1.71]; 0.004
Discontinuation due to AEs[c]	333	NA [37.82; NC] 95 (28.5)	329	NA 61 (18.5)	1.51 [1.09; 2.09]; 0.012
Severe AEs (CTCAE grade 3–4)[b]	333	244 (73.3)	329	260 (79.0)	RR: 0.93 [0.85; 1.01] 0.084[d]
Immune-related AEs				No usable data[e]	

a: HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by IMDC score (1 to 2, 3 to 6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS.
b: 100-day follow-up without recording of progression of the underlying disease.
c: 30-day follow-up without recording of progression of the underlying disease.
d: Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]). See Section 2.7.4.3 of the full dossier assessment for reasons for using the RR.
e: No usable data available; for reasons, see Section 2.7.4.3 of the full dossier assessment.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 15: Results (morbidity, health-related quality of life) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate risk)

Study Outcome category Outcome	Nivolumab + ipilimumab			Sunitinib			Nivolumab + ipilimumab vs. sunitinib
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SE)	MD [95% CI]; p-value[b]
CheckMate 214							
Morbidity							
Symptoms (FKSI-DRS)[c]	312	31.52 (3.93)	2.53 (1.06)	304	31.20 (4.41)	1.50 (1.06)	1.03 [0.58; 1.47]; < 0.001 Hedges' g: 0.36 [0.203; 0.52]
Health status (EQ-5D VAS)[c]	304	72.70 (24.57)	5.82 (6.59)	301	73.29 (25.49)	1.77 (6.58)	4.06 [1.53; 6.58]; 0.002 Hedges' g: 0.26 [0.10; 0.42]
Health-related quality of life							
FACT-G (total score)[c]	309	84.50 (13.73)	5.43 (3.00)	303	82.98 (15.07)	1.78 (3.00)	3.64 [2.05; 5.24]; < 0.001 Hedges' g: 0.36 [0.201; 0.52]
FACT-G subscales[c] (additional information)							
Physical well-being	312	24.33 (3.97)	1.80 (1.14)	306	24.29 (4.27)	−0.24 (1.14)	2.03 [1.53; 2.54]
Emotional well-being	311	17.67 (4.29)	1.84 (0.91)	306	16.93 (4.76)	1.49 (0.90)	0.35 [−0.07; 0.78]
Functional well-being	312	19.70 (5.90)	1.95 (1.27)	306	19.50 (6.04)	0.96 (1.27)	0.99 [0.34; 1.65]
Social well-being	312	22.77 (5.58)	0.56 (1.07)	307	22.32 (5.32)	0.12 (1.07)	0.43 [−0.12; 0.99]

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b: Mean and SE (change per treatment group) and MD, CI and p-value (group comparison): MMRM.
c: A positive change in comparison with baseline indicates improvement.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 16: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate risk)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Side effects					
Specific AEs					
Influenza like illness (PT, AE)	333	34 (10.2)	329	17 (5.2)	1.98 [1.13; 3.47]; 0.015
Mucosal inflammation (PT, severe AE [CTCAE grade 3–4])	333	1 (0.3)	329	10 (3.0)	0.10 [0.01; 0.77]; 0.006
Malaise (PT, AE)	333	8 (2.4)	329	21 (6.4)	0.38 [0.17; 0.84]; 0.013
Oedema (PT, AE)	333	4 (1.2)	329	18 (5.5)	0.22 [0.08; 0.64]; 0.002
Gastrointestinal disorders (SOC, AE)	333	238 (71.5)	329	287 (87.2)	0.82 [0.76; 0.89]; < 0.001
Diarrhoea (PT, SAE)	333	11 (3.3)	329	2 (0.6)	5.43 [1.21; 24.33]; 0.013
Pruritus (PT, AE)	333	126 (37.8)	329	38 (11.6)	3.28 [2.36; 4.55]; < 0.001
Rash (PT, AE)[b]	333	88 (26.4)	329	57 (17.3)	1.53 [1.13; 2.05]; 0.005
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])	333	1 (0.3)	329	25 (7.6)	0.04 [0.01; 0.29]; < 0.001
Hair colour changes (PT, AE)	333	0 (0)	329	19 (5.8)	0.03 [0.00; 0.42]; < 0.001
Yellow skin (PT, AE)[c]	333	0 (0)	329	31 (9.4)	0.02 [0.00; 0.26]; < 0.001
Arthralgia (PT, AE)	333	84 (25.2)	329	54 (16.4)	1.54 [1.13; 2.09]; 0.006
Myalgia (PT, AE)	333	51 (15.3)	329	23 (7.0)	2.19 [1.37; 3.50]; < 0.001
Pneumonia (PT, severe AE [CTCAE grade 3–4])	333	10 (3.0)	329	2 (0.6)	4.94 [1.09; 22.37]; 0.022
Pneumonitis (PT, SAE)	333	11 (3.3)	329	0 (0)	22.72 [1.34; 384.05]; < 0.001

(continued)

Table 16: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate risk) (continued)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Epistaxis (PT, AE)	333	5 (1.5)	329	46 (14.0)	0.11 [0.04; 0.27]; < 0.001
Hyperglycaemia (PT, severe AE [CTCAE grade 3–4])	333	14 (4.2)	329	3 (0.9)	4.61 [1.34; 15.89]; 0.007
Dysgeusia (PT, AE)	333	22 (6.6)	329	109 (33.1)	0.20 [0.13; 0.31]; < 0.001
Endocrine disorders (SOC, severe AE [CTCAE grade 3–4])	333	22 (6.6)	329	1 (0.3)	21.74 [2.95; 160.32]; < 0.001
Hypertension (PT, severe AE [CTCAE grade 3–4])	333	9 (2.7)	329	58 (17.6)	0.15 [0.08; 0.30]; < 0.001
Blood and lymphatic system disorders (SOC, severe AE [CTCAE grade 3–4])	333	14 (4.2)	329	44 (13.4)	0.31 [0.18; 0.56]; < 0.001

a: Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [6]); in case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
b: There is a statistically significant difference between both treatment groups to the disadvantage of nivolumab + ipilimumab for the PT "rash maculo-papular" (AE). This PT represents a similar AE as the PT "rash" and is therefore not listed separately in this table.
c: There is a significant difference between both treatment groups in favour of nivolumab + ipilimumab for the PT "skin discolouration" (AE). This PT represents a similar AE as the PT "yellow skin" and is therefore not listed separately in this table.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be derived.

The company derived the added benefit exclusively for the joint population of patients with intermediate or poor risk and did not provide separate information on the added benefit for the relevant subpopulation of patients with intermediate risk (research question 1 of the present benefit assessment). Therefore, the comments on similarities or deviations in comparison with the company's assessment of the added benefit are omitted below.

Mortality

Overall survival

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

Morbidity

Symptoms (FKSI-DRS)

The mean difference (MD) from a mixed-effects model repeated measures (MMRM) was used for the outcome "symptoms" (FKSI-DRS). A statistically significant result in favour of nivolumab + ipilimumab was shown for this outcome. The SMD in the form of Hedges' g was considered to check the relevance of the statistically significant results. The 95% CI of the SMD was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. Under consideration of the risk of bias, this resulted in a hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib for the outcome "symptoms" (FKSI-DRS).

Health status (EQ-5D VAS)

The MD from an MMRM was used for health status, measured using the EQ-5D VAS. A statistically significant difference in favour of nivolumab + ipilimumab was shown between the treatment arms. However, the 95% CI of the SMD (Hedges' g) was not completely outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. This resulted in no hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

FACT-G

The MD from an MMRM was used for the outcome "health-related quality of life" (FACT-G). A statistically significant difference in favour of nivolumab + ipilimumab was shown for the total score. The 95% CI of the SMD (Hedges' g) was completely above the irrelevance threshold of 0.2. This was interpreted to be a relevant effect. Under consideration of the risk of bias, this resulted in a hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib for the outcome "health-related quality of life" (FACT-G).

Results on side effects

Besides the superordinate outcomes "SAEs", "severe AEs" and "discontinuation due to AEs", specific AEs were also used in the benefit assessment. Specific AEs were chosen, among other aspects, based on the events that occurred in the relevant study on the basis of frequency and differences between the treatment arms and under consideration of the patient relevance. Based on this methodology, a high number of specific AEs were chosen in the present assessment. For

reasons of clarity, the results on the side effect outcomes in this specific data situation are interpreted jointly below and summarized in the weighing of positive and negative effects (see Section 2.3.3.2).

There was a high risk of bias for the results of side effect outcomes. At most hints of greater or lesser harm can therefore be derived. In few specific cases, indications can be derived (for reasons, see Section 2.7.4.2 of the full dossier assessment).

The relative risk, and not the survival time analyses, was used as effect measure for the outcomes "severe AEs" (CTCAE grade 3–4) and "specific AEs" (see Section 2.7.4.3 of the full dossier assessment).

Regarding side effect outcomes, there were both advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib.

There were statistically significant differences between the treatment arms in favour of nivolumab + ipilimumab in comparison with sunitinib in the following AEs:

- Specific AEs (AEs, SAEs, severe AEs [CTCAE grade 3–4]):
  - malaise (PT, AE)
  - mucosal inflammation (PT, severe AE [CTCAE grade 3–4])
  - gastrointestinal disorders (SOC, AE)
  - hair colour changes (PT, AE)
  - yellow skin (PT, AE)
  - oedema (PT, AE)
  - epistaxis (PT, AE)
  - dysgeusia (PT, AE)
  - palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])
  - hypertension (PT, severe AE [CTCAE grade 3–4])
  - blood and lymphatic system disorders (SOC, severe AE [CTCAE grade 3–4])

Statistically significant differences between the treatment arms to the disadvantage of nivolumab + ipilimumab in comparison with sunitinib were shown for

- SAEs
- discontinuation due to AEs
- specific AEs (AEs, SAEs, severe AEs [CTCAE grade 3–4])
  - influenza like illness (PT, AE)

- rash (PT, AE)
- arthralgia (PT, AE)
- diarrhoea (PT, SAE)
- pruritus (PT, AE)
- myalgia (PT, AE)
- pneumonia (PT, severe AE [CTCAE grade 3–4])
- pneumonitis (PT, SAE)
- hyperglycaemia (PT, severe AE [CTCAE grade 3–4])
- endocrine disorders (SOC, severe AE [CTCAE grade 3–4])

The results for the SOC "gastrointestinal disorders" (AE) and the PT "diarrhoea" (SAE) showed different directions of effects. Several PTs (irrespective of severity grade), for which – in line with the SOC – nivolumab + ipilimumab showed advantages, were included in the SOC (AE) "gastrointestinal disorders": diarrhoea, nausea, vomiting, stomatitis, dyspepsia, abdominal distension, gastrooesophageal reflux disease, toothache and sore mouth. Overall, this showed an advantage of nivolumab + ipilimumab for the SOC (AE). A disadvantage of nivolumab + ipilimumab was only shown for the PT "diarrhoea" (SAE). This PT was also included in the SOC "gastrointestinal disorders" (AE), but, due to the small number of events, had no decisive influence on the results for the SOC "gastrointestinal disorders".

No statistically significant difference between the treatment arms was shown for the outcome "severe AEs" (CTCAE grade 3–4). There were no usable data for the outcome "immune-related AEs" (see Section 2.7.4.3 of the full dossier assessment).

Overall, there were hints both of lesser and of greater harm from nivolumab + ipilimumab in comparison with sunitinib with the extents "minor" to "major". Indications of lesser or greater harm were derived for individual specific AEs (see Table 17 and Table 34 of the full dossier assessment; for reasons, see Section 2.7.4.2 of the full dossier assessment). In the overall consideration, the advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib regarding side effects were balanced. Overall, this resulted in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with sunitinib for side effects; greater or lesser harm is therefore not proven.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics, which had been prespecified in the CheckMate 214 study, were considered in the benefit assessment:

- age (< 65 years versus ≥ 65 years and < 75 years versus ≥ 75 years)
- sex (male versus female)

- region (USA versus Canada, Western Europe, Northern Europe versus rest of the world)

The subgroup characteristic "disease severity according to IMDC score" was additionally investigated in the CheckMate 214 study. This characteristic was not additionally considered using subgroup analyses as the present assessment was already conducted separately for the patient populations according to the risk profile as per the IMDC score (research question 1: intermediate risk and research question 2: poor risk).

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

Since none of the outcomes included fulfilled these criteria, the subgroup analyses are not considered.

2.3.3 Probability and extent of added benefit (research question 1)

The derivation of probability and extent of the added benefit for patients with intermediate-risk advanced renal cell carcinoma is presented 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 added benefit at outcome level (research question 1)

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.3.2.3 (see Table 17).

A detailed presentation of the extent of added benefit including the effect measures for specific AEs can be found in Table 34 in Appendix B of the full dossier assessment.

Determination of the outcome category for outcomes on symptoms and side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe. The classification of these outcomes is justified below.

Symptoms (FKSI-DRS)

The outcome "symptoms" (FKSI-DRS) was allocated to the outcome category "non-serious/ non-severe symptoms/late complications". The company provided no data that would justify the allocation of the values achieved for symptoms in the relevant subpopulation to the outcome

category “serious/severe symptoms/late complications”. The company presented no assessment regarding the severity grade of this outcome.

Discontinuation due to adverse events

The severity grade for the outcome “discontinuation due to AEs” was assessed based on the proportions of severe AEs (CTCAE grade 3–4) observed for the relevant subpopulation. Of the patients with discontinuation due to AEs in the study, > 70% had discontinuation due to severe AEs (CTCAE grade 3–4). Overall, the outcome “discontinuation due to AEs” was allocated to the severity grade category of serious/severe side effects. The company presented no assessment regarding the severity grade of this outcome.

Table 17: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate risk)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **median time to event (months) or mean or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: NA vs. 34.8 months HR: 0.70 [0.55; 0.88] p = 0.003 probability: "indication"	Outcome category: "mortality" $0.85 \leq CI_u < 0.95$ Added benefit, extent: "considerable"
Morbidity		
Symptoms (FKSI-DRS)	Mean changes: 2.5 vs. 1.5 MD: 1.03 [0.58; 1.47] p < 0.001 Hedges' g: 0.36 [0.203; 0.52][c] probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable"
Health status (EQ-5D VAS)	Mean changes: 5.8 vs. 1.8 MD: 4.06 [1.53; 6.58] p = 0.002 Hedges' g: 0.26 [0.10; 0.42][c]	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-G (total score)	Mean changes: 5.4 vs. 1.8 MD: 3.64 [2.05; 5.24] p < 0.001 Hedges' g: 0.36 [0.201; 0.52][c] probability: "hint"	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"
Side effects		
SAEs	Median: 9.1 vs. 20.8 months HR: 1.38 [1.11; 1.71] HR[d]: 0.73 [0.58; 0.901] p = 0.004 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs (CTCAE grade 3–4)	73.3% vs. 79.0% RR: 0.93 [0.85; 1.01] p = 0.084	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA vs. NA HR: 1.51 [1.09; 2.09] HR[d]: 0.66 [0.48; 0.92] p = 0.012 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"

(continued)

Table 17: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (research question 1: patients with intermediate risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **median time to event (months) or mean or proportion of events (%)** **effect estimation [95% CI]; p-value** **probability[a]**	**Derivation of extent[b]**
Specific AEs		
▪ Malaise ▪ Gastrointestinal disorders	-[e]	Lesser harm, extent: “minor”
▪ Mucosal inflammation ▪ Hair colour changes ▪ Yellow skin ▪ Oedema ▪ Epistaxis ▪ Dysgeusia	-[e]	Lesser harm, extent: “considerable”
▪ Palmar-plantar erythrodysaesthesia syndrome ▪ Hypertension ▪ Blood and lymphatic system disorders	-[e]	lesser harm, extent: “major”
▪ Influenza like illness ▪ Rash ▪ Arthralgia ▪ Pneumonia	-[e]	Greater harm, extent: “minor”
▪ Diarrhoea ▪ Pruritus ▪ Myalgia ▪ Pneumonitis ▪ Hyperglycaemia	-[e]	Greater harm, extent: “considerable”
▪ Endocrine disorders	-[e]	greater harm, extent: “major”

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size were made depending on the outcome category with different limits based on the CI_u.
c: If the CI of Hedges’ g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d: Institute’s calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: See Table 34 in Appendix B of the full dossier assessment for a detailed presentation of extent and probability of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; MD: mean difference; NA: not achieved; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.3.2 Overall conclusion on the added benefit (research question 1)

Table 25 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of nivolumab + ipilimumab in comparison with sunitinib (research question 1: patients with intermediate risk)

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: "considerable"	-
Outcome category: non-serious/non-severe symptoms/late complications Morbidity ▪ symptoms (FKSI-DRS): hint of an added benefit – extent: "non-quantifiable"	-
Outcome category: health-related quality of life ▪ FACT-G: hint of an added benefit – extent: "non-quantifiable"	-
Side effects	
Outcome categories: non-serious/severe and serious/severe side effects[a] ▪ specific AEs: ▫ 2 AEs – hint of lesser harm – extent: "minor" ▫ 6 AEs – hint of lesser harm – extent: "considerable" ▫ 3 AEs – hint of lesser harm – extent: "major"	Outcome category: serious/severe side effects ▪ overall rate of SAEs: hint of greater harm – extent: "minor" ▪ discontinuation due to AEs: hint of greater harm – extent "minor" Outcome categories: non-serious/severe and serious/severe side effects[a] ▪ specific AEs: ▫ 4 AEs – hint of greater harm – extent: "minor" ▫ 5 AEs – hint of greater harm – extent: "considerable" ▫ 1 AE – hint of greater harm – extent: "major"
a: Specific AEs include outcomes from different outcome categories. For a detailed presentation, see Table 34 in Appendix B of the full dossier assessment. AE: adverse event; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; SAE: serious adverse event	

On the positive side, there was an indication of considerable added benefit of nivolumab + ipilimumab for the outcome "overall survival" and a hint of a non-quantifiable added benefit for the outcomes "health-related quality of life" (FACT-G) and "symptoms" (FKSI-DRS).

Regarding side effects, the advantages and disadvantages of nivolumab + ipilimumab in comparison with sunitinib were balanced, so that overall there is no hint of greater or lesser harm from nivolumab + ipilimumab compared with the ACT.

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

The assessment described above deviates from the assessment of the company, which derived an indication of a major added benefit exclusively for the joint patient population with intermediate or poor-risk advanced renal cell carcinoma. The company did not provide separate information on the added benefit for the relevant subpopulation of patients with intermediate risk (research question 1 of the present benefit assessment) (see Section 2.7.1 of the full dossier assessment).

2.4 Research question 2: patients with poor risk

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 nivolumab + ipilimumab (status: 13 November 2018)
- bibliographical literature search on nivolumab + ipilimumab (last search on 6 November 2018)
- search in trial registries for studies on nivolumab + ipilimumab (last search on 13 November 2018)

To check the completeness of the study pool:

- search in trial registries for studies on nivolumab + ipilimumab (last search on 12 February 2019)

The check identified no additional relevant study.

2.4.1.1 Studies included

The study listed in Table 5 in Section 2.3.1.1 was included for research question 2 (patients with poor risk) of the present benefit assessment.

The study pool for research question 2 of the present benefit assessment of nivolumab + ipilimumab consisted of the RCT CheckMate 214 (see Table 5 in Section 2.3.1.1) and concurred with the study pool of the company.

From this study, the results of the patient population with poor risk (presence of 3 to 6 IMDC risk factors) were used for research question 2.

This deviates from the approach of the company, which used the results of patients with intermediate or poor risk as joint patient population for its assessment and derived the added

benefit exclusively for this joint patient population. The company did not provide separate information on the added benefit for the subpopulations of research question 2 of the present benefit assessment.

Section 2.6 contains a reference list for the study included.

2.4.1.2 Study characteristics

Table 6 and Table 7 in Section 2.3.1.2 describe the CheckMate 214 study used for the benefit assessment. The study design of the CheckMate 214 study is also described in Section 2.3.1.2. Table 8 presents the planned duration of follow-up observation for the individual outcomes.

Patient characteristics

Table 19 shows the characteristics of the patients with poor risk in the included study.

Table 19: Characteristics of the study population – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 2: patients with poor risk)

Study **Characteristics** **Category**	**Nivolumab + ipilimumab**	**Sunitinib**
CheckMate 214	N = 91	N = 89
Age [years], mean (SD)	61 (9)	60 (11)
Sex [F/M], %	25/75	35/65
Ethnicity, n (%)[a]		
White	79 (86.8)	78 (87.6)
Black or African American	2 (2.2)	2 (2.2)
Asian	8 (8.8)	6 (6.7)
Other	1 (1.1)	3 (3.4)
Region		
USA	26 (28.6)	26 (29.2)
Canada, Western Europe, Northern Europe	29 (31.9)	28 (31.5)
Rest of the world	36 (39.6)	35 (39.3)
Karnofsky performance status, n (%)		
100	16 (17.6)	10 (11.2)
90	26 (28.6)	25 (28.1)
80	26 (28.6)	30 (33.7)
70	22 (24.2)	23 (25.8)
< 70	1 (1.1)	1 (1.1)
Time between first diagnosis and randomization [years], n (%)		
< 1	80 (87.9)	77 (86.5)
≥ 1	11 (12.1)	12 (13.5)
Prior nephrectomy, n (%)		
Yes	57 (62.6)	57 (64.0)
No	34 (37.4)	32 (36.0)
PD-L1 status[b], n (%)		
Positive (≥ 5% tumour cell membrane staining)	20 (22.0)[c]	24 (27.0)[c]
Negative (< 5% tumour cell membrane staining)	60 (65.9)[c]	58 (65.2)[c]
Not reported	11 (12.1)	7 (7.9)
Treatment discontinuation, n (%)[d]	ND	ND
Study discontinuation, n (%)	ND	ND

(continued)

Table 19: Characteristics of the study population – RCT, direct comparison: nivolumab + ipilimumab vs. sunitinib (research question 2: patients with poor risk) (continued)

a: Ethnicity is not reported for 1 patient in the nivolumab + ipilimumab arm.
b: Determined using the Dako PD-L1 IHC 28-8 pharmDx test.
c: Information based on Institute's calculation.
d: No information available for the subpopulation of patients with poor risk. In the total population of the study, which also includes patients with favourable risk, 76.2% of the patients in the nivolumab + ipilimumab arm and 80.2% in the sunitinib arm discontinued treatment. The most common reasons for treatment discontinuation were disease progression and unacceptable toxicity.
F: female; M: male; n: number of patients in the category; N: number of randomized patients; 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 in the subpopulation with poor risk were sufficiently balanced between the study arms. Most patients were male, had a mean age of about 61 years and were of Caucasian origin. The majority of the patients in both study arms were in good general condition (Karnofsky performance status of ≥ 80).

There was no information on treatment or study discontinuation.

Course of the study

Table 20 shows the median treatment duration of the patients with poor risk and the median observation period for individual outcomes.

Table 20: Information on the course of the study – RCT, direct comparison: (research question 2: patients with poor risk)

Study **Duration of the study phase** **Outcome category**	**Nivolumab + ipilimumab**	**Sunitinib**
CheckMate 214	N = 90[a]	N = 87[a]
Treatment duration [months]		
Median[b] [min; max]	5.11 [0.0; 40.5]	3.55 [0.3; 35.5]
Observation period [months]		
Overall survival[c]		
Median [min; max]	20.80 [0.5; 40.5]	8.77 [1.2; 43.5]
Morbidity, health-related quality of life, side effects		
Median [min; max]	ND	ND

a: Information provided by the company on treatment durations and observation periods is based on the safety population.
b: Kaplan-Meier estimation; treatment durations of patients who were still receiving the study medication at the date of analysis were censored.
c: The company provides no information as to what this observation period refers to. It is assumed that this is the observation period for the outcome "overall survival".
max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The median observation period on the outcome “overall survival” in the subpopulation of patients with poor risk was more than twice as long in the nivolumab + ipilimumab arm as in the sunitinib arm. In contrast, the difference in treatment durations was less pronounced. It can be assumed that there are also no major differences between observation periods in outcomes with time points of observations that are linked to treatment duration. In the nivolumab + ipilimumab arm, the observation period estimated on the basis of treatment duration and follow-up observation was about 23% longer for such outcomes than in the sunitinib arm (see Section 2.7.4.2 of the full dossier assessment).

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 CheckMate 214 study.

2.4.2.2 Risk of bias

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 21, Table 22 and Table 23 summarize the results on the comparison of nivolumab + ipilimumab in treatment-naive adult patients with poor-risk advanced renal cell carcinoma. 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 outcomes included are presented in Appendix A, the common AEs in Appendix B of the full dossier assessment.

Table 21: Results (mortality, side effects) – RCT, direct comparison: nivolumab + ipilimumab in comparison with sunitinib (research question 2: patients with poor risk)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
CheckMate 214					
Mortality					
Overall survival	91	21.45 [15.08; 27.33] 58 (63.7)	89	9.72 [6.24; 14.32] 68 (76.4)	0.58 [0.41; 0.83]; 0.003
Side effects					
AEs (additional information)[b]	90	0.26 [0.16; 0.39] 90 (100.0)	87	0.23 [0.16; 0.30] 86 (98.9)	–
SAEs[b]	90	4.53 [2.92; 6.60] 60 (66.7)	87	4.24 [2.60; 6.28] 57 (65.5)	0.89 [0.62; 1.29]; 0.551
Discontinuation due to AEs[c]	90	NA 23 (25.6)	87	19.71 [15.21; NC] 25 (28.7)	0.73 [0.41; 1.29]; 0.272
Severe AEs (CTCAE grade 3–4)[b]	90	71 (78.9)	87	76 (87.4)	RR: 0.90 [0.79; 1.03]; 0.142[d]
Immune-related AEs	No usable data[e]				

a: HR and CI: Cox proportional hazards model, p-value: log-rank test; each stratified by IMDC score (1 to 2, 3 to 6) and region (USA, Canada/Western Europe/Northern Europe, rest of the world) according to IVRS.
b: 100-day follow-up without recording of progression of the underlying disease.
c: 30-day follow-up without recording of progression of the underlying disease.
d: Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]). See Section 2.7.4.3 of the full dossier assessment for reasons for using the RR.
e: No usable data available; for reasons, see Section 2.7.4.3 of the full dossier assessment.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IVRS: interactive voice response system; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 22: Results (morbidity, health-related quality of life) – RCT, direct comparison: nivolumab + ipilimumab in comparison with sunitinib (research question 2: patients with poor risk)

Study Outcome category Outcome	Nivolumab + ipilimumab			Sunitinib			Nivolumab + ipilimumab vs. sunitinib
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SE)	MD [95% CI]; p-value[b]
CheckMate 214							
Morbidity							
Symptoms (FKSI-DRS)[c]	80	27.80 (5.19)	3.52 (1.36)	76	26.72 (5.79)	2.70 (1.37)	0.82 [−0.30 1.94]; 0.149
Health status (EQ-5D VAS)[c]	78	63.38 (24.43)	15.02 (7.32)	74	58.98 (25.96)	13.71 (7.35)	1.31 [−3.58 6.20]; 0.598
Health-related quality of life							
FACT-G (total score)[c]	80	76.15 (17.37)	6.53 (3.57)	77	72.67 (15.96)	4.54 (3.59)	2.00 [−1.74; 5.73]; 0.293
FACT-G subscales[c] (additional information)							
Physical well-being	80	20.68 (5.55)	2.96 (1.42)	77	20.44 (5.39)	0.72 (1.42)	2.24 [0.99; 3.49]
Emotional well-being	80	17.23 (4.58)	1.08 (1.11)	77	16.06 (4.65)	0.98 (1.12)	0.10 [−0.85; 1.05]
Functional well-being	80	15.52 (7.31)	2.84 (1.51)	77	14.00 (7.03)	2.07 (1.52)	0.77 [−0.70; 2.25]
Social well-being	80	22.71 (3.97)	1.08 (1.28)	77	22.16 (5.26)	1.90 (1.28)	−0.82 [−1.90; 0.26]

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline may be based on other patient numbers.
b: Mean and SE (change per treatment group) and MD, CI and p-value (group comparison): MMRM.
c: A positive change in comparison with the start of the study indicates improvement.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 23: Results (side effects) – RCT, direct comparison: nivolumab + ipilimumab in comparison with sunitinib (research question 2: patients with poor risk)

Study Outcome category Outcome	Nivolumab + ipilimumab		Sunitinib		Nivolumab + ipilimumab vs. sunitinib
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Side effects					
Specific AEs					
Stomatitis (PT, AE)	90	2 (2.2)	87	15 (17.2)	0.13 [0.03; 0.55]; < 0.001
Fever (PT, AE)	90	26 (28.9)	87	9 (10.3)	2.79 [1.39; 5.61]; 0.002
Mucosal inflammation (PT, AE)	90	1 (1.1)	87	25 (28.7)	0.04 [0.01; 0.28]; < 0.001
Epistaxis (PT, AE)	90	1 (1.1)	87	9 (10.3)	0.11 [0.01; 0.83]; 0.008
Pruritus (PT, AE)	90	22 (24.4)	87	7 (8.0)	3.04 [1.37; 6.75]; 0.003
Palmar-plantar erythrodysaesthesia syndrome (PT, severe AE [CTCAE grade 3–4])	90	0 (0)	87	7 (8.0)	-[b]; 0.007
Dysgeusia (PT, AE)	90	7 (7.8)	87	24 (27.6)	0.28 [0.13; 0.62]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	90	8 (8.9)	87	17 (19.5)	0.45 [0.21; 0.999]; 0.044
Hypothyroidism (PT, AE)	90	5 (5.6)	87	16 (18.4)	0.30 [0.12; 0.79]; 0.009
Ear and labyrinth disorders (SOC, AE)	90	9 (10.0)	87	2 (2.3)	-[b]; 0.036
Gastrointestinal disorders (SOC, severe AE [CTCAE grade 3–4])	90	7 (7.8)	87	17 (19.5)	0.40 [0.17; 0.91]; 0.024
Thrombocytopenia (PT, severe AE [CTCAE grade 3–4])	90	0 (0)	87	7 (8.0)	-[b]; 0.007

a: Institute's calculation of RR and CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [6]); in case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.

b: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; effect estimation and CI not presented because not informative.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, at most indications, e.g. of an added benefit, can be determined for all outcomes.

The company derived the added benefit exclusively for the joint population of patients with intermediate or poor risk and did not provide separate information on the added benefit for the relevant subpopulation of patients with poor risk (research question 2 of the present benefit assessment). Therefore, the comments on similarities or deviations in comparison with the company's assessment of the added benefit are omitted below.

Mortality

Overall survival

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

Morbidity

Symptoms (FKSI-DRS)

The MD from an MMRD was used for the outcome "symptoms" (FKSI-DRS). There was no statistically significant difference between the treatment arms for this outcome. This resulted in no hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

The MD from an MMRM was used for health status, measured using the EQ-5D VAS. There was no statistically significant difference between the treatment arms for this outcome. This resulted in no hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib; an added benefit is therefore not proven.

Health-related quality of life

FACT-G

The MD from an MMRM was used for the outcome "health-related quality of life" (FACT-G). There was no statistically significant difference between the treatment arms for this outcome. This resulted in no hint of an added benefit of nivolumab + ipilimumab in comparison with sunitinib; an added benefit is therefore not proven.

Side effects

Serious adverse events

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

Severe adverse events (CTCAE grade 3–4)

The relative risk, and not the survival time analysis, was used as effect measure for the outcome "severe AEs" (CTCAE grade 3–4) (see Section 2.7.4.3 of the full dossier assessment). There was no statistically significant difference between the treatment arms. This resulted in no hint of greater or lesser harm from nivolumab + ipilimumab in comparison with sunitinib; greater or lesser harm is therefore not proven.

Discontinuation due to adverse events

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

Specific adverse events

The relative risk, and not the survival time analysis, was used as effect measure for the specific AEs (AEs, SAEs, severe AEs [CTCAE grade 3–4]) (for reasons, see Section 2.7.4.3 of the full dossier assessment).

Statistically significant differences between the treatment arms in favour of nivolumab + ipilimumab in comparison with sunitinib were shown for the following outcomes: stomatitis, mucosal inflammation, epistaxis, palmar-plantar erythrodysaesthesia syndrome, dysgeusia, respiratory, thoracic and mediastinal disorders, hypothyroidism, gastrointestinal disorders, and thrombocytopenia. Under consideration of the risk of bias, this resulted in a hint of lesser harm of nivolumab + ipilimumab in comparison with sunitinib for individual outcomes.

There were statistically significant differences between the treatment arms to the disadvantage of nivolumab + ipilimumab in comparison with sunitinib for the outcomes "fever", "pruritus" and "ear and labyrinth disorders". Under consideration of the risk of bias, this resulted in a hint of greater harm of nivolumab + ipilimumab in comparison with sunitinib for individual outcomes.

Immune-related adverse events

There were no usable data for the outcome "immune-related AEs" (see Section 2.7.4.3 of the full dossier assessment).

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics, which had been prespecified in the CheckMate 214 study, were considered in the benefit assessment:

- age (< 65 years versus ≥ 65 years and < 75 years versus ≥ 75 years)
- sex (male versus female)
- region (USA versus Canada, Western Europe, Northern Europe versus rest of the world)

The subgroup characteristic “disease severity according to IMDC score” was additionally investigated in the CheckMate 214 study. This characteristic was not additionally considered using subgroup analyses as the present assessment was already conducted separately for the patient populations according to the risk profile as per the IMDC score (research question 1: intermediate risk and research question 2: poor risk).

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

Since none of the outcomes included fulfilled these criteria, the subgroup analyses are not considered.

2.4.3 Probability and extent of added benefit (research question 2)

The derivation of probability and extent of the added benefit for patients with poor-risk advanced renal cell carcinoma (research question 2) is presented 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 added benefit at outcome level (research question 2)

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.2.3 (see Table 24).

Table 24: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (research question 2: patients with poor risk)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: 21.5 vs. 9.7 months HR: 0.58 [0.41; 0.83] p = 0.003 probability: “indication”	Outcome category: “mortality” $CI_u < 0.85$ Added benefit, extent: “major”
Morbidity		
Symptoms (FKSI-DRS)	Mean changes: 3.5 vs. 2.7 MD: 0.82 [−0.30; 1.94] p = 0.149	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	Mean changes: 15.0 vs. 13.7 MD: 1.31 [−3.58; 6.20] p = 0.598	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-G (total score)	Mean changes: 6.5 vs. 4.5 MD: 2.00 [−1.74; 5.73]; p = 0.293	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 4.5 vs. 4.2 months HR: 0.89 [0.62; 1.29] p = 0.551	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	78.9% vs. 87.4% RR: 0.90 [0.79; 1.03] p = 0.142	Greater/lesser harm not proven
Discontinuation due to AEs	Median: NA vs. 19.7 months HR: 0.73 [0.41; 1.29]; p = 0.272	Greater/lesser harm not proven
Stomatitis	2.2% vs. 17.2% RR: 0.13 [0.03; 0.55]; p < 0.001 probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: “considerable”

(continued)

Table 24: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (research question 2: patients with poor risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Fever	28.9% vs. 10.3% RR: 2.79 [1.39; 5.61] RR[c]: 0.36 [0.18; 0.72] p = 0.002 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Mucosal inflammation	1.1% vs. 28.7% RR: 0.04 [0.01; 0.28]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Epistaxis	1.1% vs. 10.3% RR: 0.11 [0.01; 0.83]; p = 0.008 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Lesser harm, extent: "minor"
Pruritus	24.4% vs. 8.0% RR: 3.04 [1.37; 6.75] RR[c]: 0.33 [0.15; 0.73] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Palmar-plantar erythrodysaesthesia syndrome	0.0% vs. 8% RR: -[d] p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe side effects lesser harm, extent: "non-quantifiable"
Dysgeusia	7.8% vs. 27.6% RR: 0.28 [0.13; 0.62]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders	8.9% vs. 19.5% RR: 0.45 [0.21; 0.999]; p = 0.044 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.0$ Lesser harm, extent: "minor"

(continued)

Table 24: Extent of added benefit at outcome level: nivolumab + ipilimumab vs. sunitinib (research question 2: patients with poor risk) (continued)

Outcome category **Outcome**	**Nivolumab + ipilimumab vs. sunitinib** **Median of time to event (months) or mean** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Hypothyroidism	5.6% vs. 18.4% RR: 0.30 [0.12; 0.79]; p = 0.009 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Ear and labyrinth disorders	10% vs. 2.3% RR: -[d] p = 0.036 probability: "hint"	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"
Gastrointestinal disorders	7.8% vs. 19.5% RR: 0.40 [0.17; 0.91] p = 0.024 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.0$ Lesser harm, extent: "minor"
Thrombocytopenia	0% vs. 8% RR: -[d] p = 0.007 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category 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.
d: Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods; effect estimation and CI not presented because not informative.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-G: Functional Assessment of Cancer Therapy-General; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; MD: mean difference; NC: not calculable; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on the added benefit (research question 2)

Table 25 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 25: Positive and negative effects from the assessment of nivolumab + ipilimumab in comparison with sunitinib (research question 2: patients with poor risk)

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: "major"	-
Outcome categories: non-serious/severe and serious/severe side effects[a] specific AEs: ▪ stomatitis: hint of lesser harm – extent: "considerable" ▪ mucosal inflammation: hint of lesser harm – extent: "considerable" ▪ epistaxis: hint of lesser harm – extent: "minor" ▪ palmar-plantar erythrodysaesthesia syndrome: hint of lesser harm – extent: "non-quantifiable" ▪ dysgeusia: hint of lesser harm – extent: "considerable" ▪ respiratory, thoracic and mediastinal disorders: hint of lesser harm – extent: "minor" ▪ hypothyroidism: hint of lesser harm – extent: "considerable" ▪ gastrointestinal disorders: hint of lesser harm – extent: "minor" ▪ thrombocytopenia: hint of lesser harm – extent: "non-quantifiable"	Outcome categories: non-serious/severe and serious/severe side effects[a] specific AEs: ▪ fever: hint of greater harm – extent: "considerable" ▪ pruritus: hint of greater harm – extent: "considerable" ▪ ear and labyrinth disorders: hint of greater harm – extent: "non-quantifiable"
a: Specific AEs include outcomes from different outcome categories. For a detailed presentation, see Table 34 in Appendix B of the full dossier assessment. AE: adverse event	

In the overall assessment, there are both positive and negative effects with different certainty of results (indication or hint) for nivolumab + ipilimumab in comparison with sunitinib in patients with poor-risk advanced renal cell carcinoma.

An indication of a major added benefit was shown for the outcome "overall survival". Furthermore, hints of lesser harm with different extents were shown for a number of outcomes of the category of side effects with different severity grades.

On the negative side, there were hints of greater harm with different extents of nivolumab + ipilimumab versus sunitinib for 3 outcomes of the category of side effects.

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

The assessment described above deviates from the assessment of the company, which derived an indication of a major added benefit exclusively for the joint patient population with

intermediate or poor-risk advanced renal cell carcinoma. The company did not provide separate information on the added benefit for the relevant subpopulation of patients with poor risk (research question 2 of the present benefit assessment) (see Section 2.7.1 of the full dossier assessment).

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of nivolumab + ipilimumab in comparison with the ACT is summarized in Table 26.

Table 26: Nivolumab + ipilimumab – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
1	Treatment-naive adult patients with intermediate-risk advanced renal cell carcinoma (1−2 risk factors as per the IMDC criteria)	Bevacizumab in combination with interferon alfa-2a or monotherapy with pazopanib or **sunitinib**	Indication of considerable added benefit[b]
2	Treatment-naive adult patients with poor-risk advanced renal cell carcinoma (≥ 3 risk factors as per the IMDC criteria)	Temsirolimus or **sunitinib**	Indication of a major 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 CheckMate 214 study underlying the benefit assessment did not investigate patients with non-clear cell renal cell carcinoma, advanced AJCC stage III renal cell carcinoma, brain metastases, or Karnofsky performance status < 70% (see Section 2.7.4.1 of the full dossier assessment). It is unclear whether the observed effects are transferable to patients with the characteristics described above.
ACT: appropriate comparator therapy; AJCC: American Joint Committee on Cancer; 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

Bristol-Myers Squibb. Nivolumab program: protocols CA209; core safety statistical analysis plan for multiple indications; version 5 [unpublished].

Bristol-Myers Squibb. A phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma [online]. In: EU Clinical Trials Register. [Accessed: 15.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001750-42.

Bristol-Myers Squibb. Nivolumab combined with ipilimumab versus sunitinibin previously untreated advanced or metastatic renal cell carcinoma (CheckMate 214): study results [online]. In: ClinicalTrials.gov. 16.10.2018 [Accessed: 15.02.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02231749.

Bristol-Myers Squibb. A phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma: study CA209214; statistical analysis plan; version 3.0 [unpublished]. 2016.

Bristol-Myers Squibb. A phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma: study CA209214; final clinical study report [unpublished]. 2017.

Bristol-Myers Squibb. A phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma (CheckMate 214, checkpoint pathway and nivolumab clinical trial evaluation 214): study CA209214; interim clinical study report [unpublished]. 2017.

Bristol-Myers Squibb. A phase 3, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated, advanced or metastatic renal cell carcinoma (CheckMate 214, checkpoint pathway and nivolumab clinical trial evaluation 214): study CA209214; clinical protocol [unpublished]. 2017.

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Goethe University Frankfurt. A phase 2, randomized, open-label study of nivolumab combined with ipilimumab versus standard of care in subjects with previously untreated and advanced (unresectable or metastatic) non-clear cell renal cell carcinoma [online]. In: EU Clinical Trials Register. [Accessed: 15.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000706-12.

Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018; 378(14): 1277-1290.

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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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