IQWiG Reports – Commission No. A21-49

Cabozantinib (renal cell carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Cabozantinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 1 October 2021). 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Cabozantinib (renal cell carcinoma) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
29 April 2021

Internal Commission No.
A21-49

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Ingo Schmidt-Wolf, University Hospital Bonn, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment

- Anne-Kathrin Petri
- Charlotte Hecker
- Marco Knelangen
- Sabine Ostlender
- Regine Potthast
- Sonja Schiller
- Anke Schulz
- Volker Vervölgyi

Keywords: Cabozantinib, Nivolumab, Carcinoma – Renal Cell, Benefit Assessment, NCT 03141177, NCT02853331

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 figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American-Joint-Committee-on-Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CTLA 4	cytotoxic T-lymphocyte-associated antigen 4
EMA	European Medicines Agency
FKSI-DRS	Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KPS	Karnofsky performance status
PD-1	programmed cell death protein1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics (SPC)
TKI	tyrosine kinase inhibitors
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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 cabozantinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 April 2021.

Research question

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

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

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

Research question	Therapeutic indication	ACT[a]
1	Adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0)	▪ Pembrolizumab in combination with axitinib
2	Adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)[b]	▪ Avelumab in combination with axitinib (only for patients with poor risk profile) or ▪ nivolumab in combination with ipilimumab or ▪ **pembrolizumab in combination with axitinib**

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 G-BA pointed out that the two risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Before this background, subgroup analyses for patients with intermediate and poor risk profiles were to be presented in the dossier.

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

The company deviates from the G-BA's specification of the ACT. It also named the options specified by the G-BA and selected pembrolizumab in combination with axitinib (hereafter referred to as "pembrolizumab + axitinib") as ACT for both research questions. However, deviating from the G-BA's specification, the company additionally used sunitinib as ACT. This deviation is not appropriate. The company did not cite any sources that adequately justify the additional consideration of sunitinib in the framework of the appropriate comparator therapy.

Each of the ACT options cited by the G-BA showed considerable added benefit versus sunitinib. This is also reflected in the German S3 guideline, which recommends sunitinib only if a checkpoint inhibitor-based combination therapy cannot be performed. The present benefit assessment of cabozantinib + nivolumab was conducted versus the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Research question 1: Adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0)

Study pool and study design

For research question 1, no randomized controlled trial (RCT) of direct comparison was identified for the assessment of the added benefit of cabozantinib + nivolumab. The company presented an adjusted indirect comparison using the common comparator sunitinib with the study CA209-9ER (hereinafter referred to as "CheckMate 9ER") on the cabozantinib + nivolumab side and the study KEYNOTE-426 on the pembrolizumab + axitinib side.

Study CheckMate 9ER (study with cabozantinib + nivolumab)

The CheckMate 9ER study was a randomized, open-label, active-controlled approval study on the comparison of cabozantinib + nivolumab with sunitinib. The study included adults with advanced or metastatic RCC (stage IV according to the American-Joint-Committee-on-Cancer[AJCC] classification) with clear-cell component. The patients were not allowed to have received any prior systemic therapy for advanced disease; adjuvant or neoadjuvant therapy was allowed. The patients were to be in good general condition (Karnofsky performance status [KPS] ≥ 70%). Patients with RCC without a clear-cell component, with a KPS < 70% or with active brain metastases were excluded from participation in the study; hence, no data are available for them.

The study included patients regardless of their risk profile. However, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score in the study was recorded as a disease characteristic at the start of the study so that it was possible to differentiate patients based on their risk profile according to the IMDC score.

Overall, 651 patients were randomly allocated in a 1:1 ratio either to treatment with cabozantinib + nivolumab (N = 323) or to sunitinib (N = 328).

The primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status and adverse events (AEs).

There were two data cut-offs for the CheckMate 9ER study. The results of the second data cut-off of 10 September 2020 were used for the benefit assessment.

Relevant subpopulation of the CheckMate 9ER study

The subpopulation of patients with favourable risk profile (IMDC score 0) of the CheckMate 9ER study is relevant for research question 1. These were 74 patients in the cabozantinib + nivolumab arm and 72 patients in the sunitinib arm. In Module 4 D, the company presented analyses for this subpopulation.

Study KEYNOTE-426 (study with pembrolizumab + axitinib)

The KEYNOTE-426 study is a randomized, open-label, active-controlled approval study on the comparison of pembrolizumab + axitinib with sunitinib. The study included adults with advanced or metastatic clear-cell RCC (stage IV according to the AJCC classification). The patients were not allowed to have received any prior systemic therapy for advanced disease; any adjuvant or neoadjuvant therapy had to be completed 12 months before the start of the study. The patients were to be in good general condition (KPS ≥ 70%). Patients with non-clear cell RCC, with a KPS < 70 % or with active brain metastases were excluded from participation in the study; hence, no data are available for them.

The study included patients regardless of their risk profile. However, the IMDC score in the study was recorded as a disease characteristic at the beginning of the study so that it is possible to differentiate patients based on their risk profile according to the IMDC score.

Overall, 861 patients were randomly allocated in a 1:1 ratio either to treatment with pembrolizumab + axitinib (N = 432) or to sunitinib (N = 429).

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

There were 3 data cut-offs for the KEYNOTE-426 study. If available, the data of the third data cut-off at 6 January 2020 were primarily used for the present benefit assessment.

Relevant subpopulation of the KEYNOTE-426 study

The subpopulation of patients with favourable risk profile (IMDC score 0) of the KEYNOTE-426 study is relevant for research question 1. These were 138 patients in the pembrolizumab + axitinib arm and 131 patients in the sunitinib arm. In Module 4 D, the company presented analyses for this subpopulation.

Similarity of the relevant subpopulations of the studies CheckMate 9ER and KEYNOTE-426 not assessable due to limited information

The two studies CheckMate 9ER and KEYNOTE-426 included patients regardless of their risk profile. The subpopulation of patients with favourable risk profile relevant to research question 1 only accounts for a small proportion of the total population in both studies, 22% (CheckMate 9ER) and 31% (KEYNOTE-426).

Information on the patient characteristics of the subpopulation relevant for research question 1 (favourable risk profile) is only available for the CheckMate 9ER study. Corresponding data are missing for KEYNOTE-426. Since, in contrast to the CheckMate 9ER study, there is no information on the subpopulation with an intermediate or poor risk profile for the KEYNOTE-426 study (research question 2), it cannot be deduced (also indirectly) with sufficient certainty that the subpopulation of the KEYNOTE-426 study is sufficiently similar to that of the CheckMate 9ER study.

Regardless of this and analogous to question 2, the indirect comparison between the two studies CheckMate 9ER and KEYNOTE-426 allowed no conclusions on the added benefit for the outcomes of the categories "morbidity", "health-related quality of life" and "side effects". This means that even if the similarity between the two studies CheckMate 9ER and KEYNOTE-426 were assumed to be given for research question 1, only the outcome "overall survival" would be evaluable - as with research question 2. Considering the results presented for the outcome "overall survival", there was no statistically significant difference between cabozantinib + nivolumab and pembrolizumab + axitinib for the relevant subpopulation of research question 1 (favourable risk profile).

Results

The company presented no suitable data for the assessment of the added benefit of cabozantinib + nivolumab in comparison with the ACT in adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0). This resulted in no hint of an added benefit of cabozantinib + nivolumab in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)

Study pool and study design

For research question 2, no RCT of direct comparison was identified for the assessment of the added benefit of cabozantinib + nivolumab. The company presented an adjusted indirect comparison using the common comparator sunitinib with the study CheckMate 9ER on the cabozantinib + nivolumab side and the study KEYNOTE-426 on the pembrolizumab + axitinib side.

Study CheckMate 9ER (study with cabozantinib + nivolumab)

The information on CheckMate 9ER is described in research question 1.

Relevant subpopulation

The subpopulation of patients with intermediate or poor risk profile (IMDC score 1 to 6) of the CheckMate 9ER study is relevant for research question 2. This subpopulation comprised 249 patients in the cabozantinib + nivolumab arm and 256 patients in the sunitinib arm.

Study KEYNOTE-426 (study with pembrolizumab + axitinib)

The information on KEYNOTE-426 is described in research question 1.

Relevant subpopulation

The subpopulation of patients with intermediate or poor risk profile (IMDC score 1 to 6) of the KEYNOTE-426 study is relevant for research question 2. This subpopulation comprised 294 patients in the pembrolizumab + axitinib arm and 298 patients in the sunitinib arm.

Similarity of the studies for the indirect comparison

The check of the similarity of the studies CheckMate 9ER and KEYNOTE 426 revealed a number of ambiguities or uncertainties regarding the similarity of the studies presented for the indirect comparison. These uncertainties are primarily due to the missing data for the relevant data cut-offs and for the populations according to the research questions relevant for the present benefit assessment. However, these differences do not lead to a fundamental questioning of the similarity of the studies.

Risk of bias

The risk of bias across outcomes was rated as low in both studies.

Usable data for the adjusted indirect comparison of the studies CheckMate 9ER and KEYNOTE-426 were only available for the results on the outcome "overall survival". The risk of bias at study level was rated as low.

There were no or only unusable data for the outcomes "symptoms", "health status", "health-related quality of life", "immune-related serious adverse events (SAEs)" and "immune-related severe AES". Therefore, the risk of bias was not assessed for these outcomes.

The risk of bias of the results on the outcome "discontinuation due to AEs" was rated as high due to the open-label study design. The risk of bias of each of the results on the superordinate outcome "severe AEs" and "SAEs" is high due to incomplete observations for potentially informative reasons.

Due to the high risk of bias of the results on "discontinuation due to AEs", "discontinuation due to severe AEs" and "discontinuation due to SAEs", there is no sufficient certainty of results to meet the minimum requirements for the certainty of results for the derivation of a hint in the indirect comparison.

There was one RCT on each side of the available adjusted indirect comparison. Hence, a check of the homogeneity assumption was not required. As there was no study of direct comparison of cabozantinib + nivolumab versus the ACT, the consistency assumption could not be checked. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived based on the data available from the adjusted indirect comparison.

Results

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; an added benefit is therefore not proven.

Morbidity

The studies CheckMate 9ER and KEYNOTE-426 provide no usable data on the outcomes of the category "morbidity". Hence, there was no hint of an added benefit of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; an added benefit is therefore not proven.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the CheckMate 9ER study. Therefore, an adjusted indirect comparison is no possible. Hence, there was no hint of an added benefit of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; an added benefit is therefore not proven.

Side effects

Due to insufficient certainty of results in both studies, an indirect comparison was not possible for the outcomes "SAEs", "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" and "discontinuation due to AEs". There were no usable data for the outcomes "immune-related SAEs" and "immune-related severe AEs" (CTCAE grade ≥ 3). This resulted in no hint of greater or lesser harm from cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; greater or lesser harm is therefore not proven.

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

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

[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].

Research question 1: Adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0)

Since the company presented no suitable data for the assessment of cabozantinib + nivolumab versus the ACT in adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0), the added benefit of cabozantinib + nivolumab is not proven for these patients.

Research question 2: Adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)

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

Overall, based on the adjusted indirect comparison using the common comparator sunitinib, there are neither positive nor negative effects of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib for research question 2.

However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are only available for the outcome "overall survival". There is no hint of an added benefit of cabozantinib + nivolumab for this outcome, as the indirect comparison showed no statistically significant difference. There were no or no usable data or the outcomes of the outcome categories "morbidity" and "health-related quality of life". No usable data for an indirect comparison are available for the outcome category of side effects, as the certainty of results was not sufficient for an indirect comparison. An adequate balancing of benefit and harm is impossible due to the lack of usable results on these outcome categories.

In summary, there was no hint of an added benefit of cabozantinib + nivolumab versus pembrolizumab + axitinib for adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1 to 2) or poor risk profile (IMDC score ≥ 3).

Table 3 shows a summary of the probability and extent of the added benefit of cabozantinib + nivolumab.

Table 3: Cabozantinib + nivolumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven[c]
2	Adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)[b]	Pembrolizumab in combination with axitinib ▪ avelumab in combination with axitinib (only for patients with poor risk profile) or ▪ nivolumab in combination with ipilimumab or ▪ **pembrolizumab in combination with axitinib**	Added benefit not proven[c]

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 G-BA pointed out that the two risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Before this background, subgroup analyses for patients with intermediate and poor risk profiles were to be presented in the dossier.
c. The studies CheckMate 9ER and KEYNOTE-426 only included patients with RCC with clear-cell component and a Karnofsky performance status ≥ 70%. It remains unclear whether the observed effects can be transferred to patients without clear-cell component and a Karnofsky performance status < 70 %.

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

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of cabozantinib in combination with nivolumab (hereinafter referred to as "cabozantinib + nivolumab") in comparison with the ACT in adult patients with treatment-naive advanced RCC.

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

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

Research question	Therapeutic indication	ACT[a]
1	Adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0)	▪ Pembrolizumab in combination with axitinib
2	Adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)[b]	▪ Avelumab in combination with axitinib (only for patients with poor risk profile) or ▪ nivolumab in combination with ipilimumab or ▪ **pembrolizumab in combination with axitinib**

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 G-BA pointed out that the two risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Before this background, subgroup analyses for patients with intermediate and poor risk profiles were to be presented in the dossier.

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

The company deviates from the G-BA's specification of the ACT. It also named the options specified by the G-BA and selected pembrolizumab in combination with axitinib (hereafter referred to as "pembrolizumab + axitinib") as ACT for both research questions. However, deviating from the G-BA's specification, the company additionally used sunitinib as ACT. This deviation is not appropriate. The company did not cite any sources that adequately justify the additional consideration of sunitinib in the framework of the appropriate comparator therapy. Each of the ACT options cited by the G-BA showed considerable added benefit versus sunitinib [3-5]. This is also reflected in the German S3 guideline, which recommends sunitinib only if a checkpoint inhibitor-based combination therapy cannot be performed [6]. The present benefit assessment of nivolumab + cabozantinib was conducted versus the G-BA's ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Research question 1: Adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0)

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 cabozantinib + nivolumab (status: 6 March 2021)

- bibliographical literature search on cabozantinib + nivolumab (last search on 1 March 2021)
- search in trial registries/trial results databases for studies on cabozantinib + nivolumab (last search on 1 March 2021)
- search on the G-BA website for cabozantinib + nivolumab (last search on 9 March 2021)
- bibliographical literature search on the ACT (last search on 1 March 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 1 March 2021)
- search on the G-BA website for the ACT (last search on 9 March 2021)

To check the completeness of the study pool:

- search in trial registries for studies on cabozantinib + nivolumab (last search on 19 May 2021); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 11 June 2021); for search strategies, see Appendix A of the full dossier assessment

Direct comparison

Concurring with the company, no relevant RCT on the direct comparison of cabozantinib + nivolumab versus the ACT specified by the G-BA was identified.

However, deviating from this approach, the company used the CheckMate 9ER study as direct comparator study of cabozantinib + nivolumab versus sunitinib for the derivation of the added benefit (see Section 2.2).

Indirect comparison

As the company identified no RCTs versus one of the ACT options specified by the G-BA, it searched for RCTs for an adjusted indirect comparison. In doing so, it first searched for RCTs with the intervention "nivolumab + cabozantinib" to be assessed and identified one relevant RCT on the comparison with sunitinib:

- CA209-9ER (CheckMate 9ER): cabozantinib + nivolumab vs. sunitinib [7]

For the indirect comparison, the company conducted an information retrieval on studies with the ACT and the common comparator sunitinib. The restriction to sunitinib as a common comparator is appropriate, as the check of the completeness of the study pool identified no further relevant RCT with cabozantinib + nivolumab and thus no further relevant common comparator for a possible adjusted indirect comparison.

On the side of the ACT, the company identified the following study for pembrolizumab + axitinib:

- KEYNOTE 426: pembrolizumab + axitinib vs. sunitinib [8,9]

Concurring with the company, the check of the completeness of the study pool identified no relevant study on the comparison of pembrolizumab + axitinib vs. sunitinib.

2.3.2 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib (research questions 1 and 2

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
Cabozantinib + nivolumab vs. sunitinib						
CA209-9ER (CheckMate 9ER[d])	Yes	Yes	No	No[e]	Yes [10-12]	Yes [7]
Pembrolizumab + axitinib vs. sunitinib						
KEYNOTE-426	No	No	Yes	No	Yes [13-16]	Yes [3,8,9,17,18]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool concurs with that of the company. KEYNOTE-426 had already been submitted and assessed for a previous benefit assessment of pembrolizumab + axitinib (A19-99) [19].

Figure 1 shows a schematic representation of the indirect comparison.

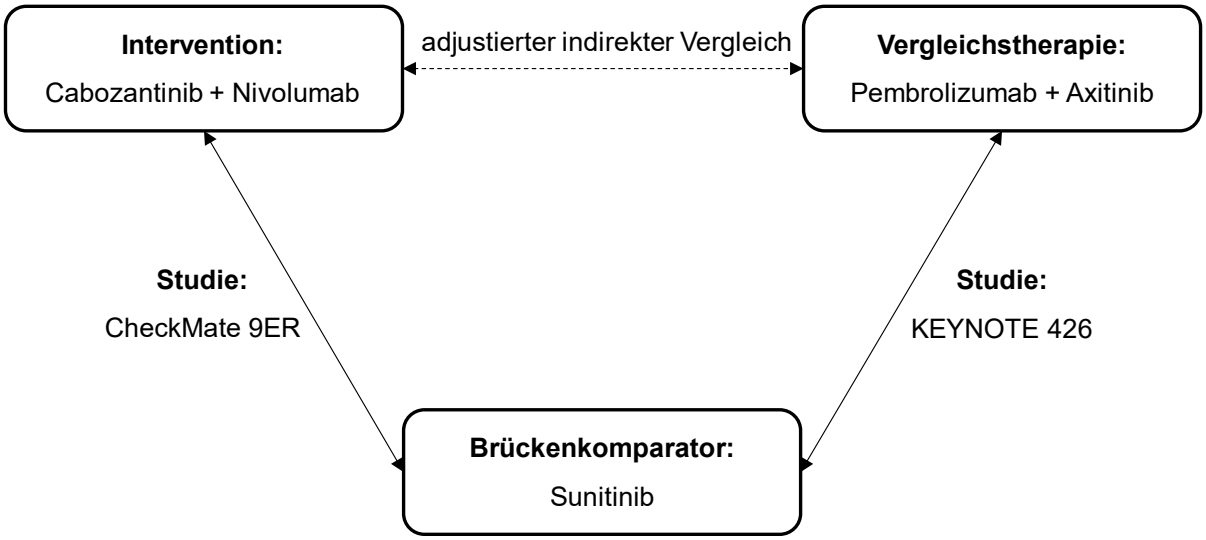

Figure 1: Study pool of the company for the indirect comparison of cabozantinib + nivolumab versus pembrolizumab + axitinib, research questions 1 and 2

Intervention: cabozantinib + nivolumab
Adjusted indirect comparison
Comparator therapy: pembrolizumab + axitinib
Study: CheckMate 9 ER
Study: KEYNOTE-426
Common comparator: sunitinib

2.3.3 Study characteristics

2.3.3.1 Study design

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

Table 6: Characteristics of the included studies – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib (research questions 1 and 2) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Cabozantinib + nivolumab vs. sunitinib						
CheckMate 9ER	RCT, open-label, parallel	Adults with treatment-naive advanced or metastatic RCC[b] (AJCC stage IV) and Karnofsky performance status ≥ 70%	Cabozantinib + nivolumab (N = 323) cabozantinib + nivolumab + ipilimumab (N = 50[c]) sunitinib (N = 328) relevant subpopulations thereof: <u>research question 1:</u> patients with favourable risk profile (IMDC score 0) cabozantinib + nivolumab (n = 74) sunitinib (n = 72) <u>research question 2:</u> patients with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3) cabozantinib + nivolumab (n = 249) sunitinib (n = 256)	Screening: ND treatment: until disease progression, unacceptable toxicity or treatment discontinuation following the decision by the physician or the patient; nivolumab was not allowed to be administered for more than 2 years observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	125 centres in Argentina, Australia, Brazil, Chile, Czech Republic, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Romania, Spain, Turkey, United Kingdom, USA 08/2017–ongoing <u>data cut-offs:</u> 30 March 2020 (first interim analysis for OS[e] and final analysis for PFS) 10 September 2020 (second OS interim analysis[f])	Primary: PFS secondary: overall survival, symptoms, health status, AEs

Table 6: Characteristics of the included studies – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib (research questions 1 and 2) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Pembrolizumab + axitinib vs. sunitinib						
KEYNOTE-426	RCT, open-label, parallel	Adults with treatment-naive advanced or metastatic RCC[b] (AJCC stage IV) and Karnofsky performance status ≥ 70%	Pembrolizumab + axitinib (N = 432) sunitinib (n = 429) relevant subpopulations thereof: <u>research question 1:</u> patients with favourable risk profile (IMDC score 0) pembrolizumab + axitinib (N = 138) sunitinib (n = 131) <u>research question 2:</u> patients with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3): pembrolizumab + axitinib (N = 294) sunitinib (n = 298)	Screening: ≤ 28 days treatment: until disease progression, unacceptable toxicity or treatment discontinuation following the decision by the physician or the patient; pembrolizumab was not allowed to be administered for more than 35 cycles (2 years)[g] observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	129 centres in Brazil, Canada, Czech Republic, France, Germany, Great Britain, Hungary, Ireland, Japan, Poland, Russia, South Korea, Spain, Taiwan, Ukraine, USA 10/2016–ongoing <u>data cut-offs:</u> 24 August 2018 (prespecified, first interim analysis)[h] 2 January 2019 (post-hoc analysis)[i] 6 January 2020[j] (prespecified, second interim analysis)	Primary: overall survival, PFS secondary: symptoms, health status, health-related quality of life, AEs

Table 6: Characteristics of the included studies – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib (research questions 1 and 2) (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
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. histologically confirmed RCC with clear-cell component including sarcomatoid features. c. The original protocol of the CheckMate 9ER study had planned the inclusion of patients in a third study arm for the investigation of the triple combination of nivolumab, ipilimumab and cabozantinib. The inclusion of patients in this treatment arm was stopped with the first review of the study protocol. Due to the lack of relevance for the research question, this study arm is no longer presented in the following tables. d. Outcome-specific information is provided in Table 8. e. Planned for the time when 165 deaths were detected. f. Planned for the time when 211 deaths were detected. g. With a complete, confirmed response or after reaching the maximum treatment duration in stable disease, patients after subsequent confirmed progression could resume treatment with pembrolizumab for another year ("second course phase"). h. Planned for the time at which at least 305 PFS events have occurred and all patients have undergone follow-up observation for at least 7 months after randomization. i. Upon request by the EMA. j. Planned for the time at which 74% of the final required OS events (or 299 deaths) have occurred. AJCC: American Joint Committee on Cancer; EMA: European Medicines Agency; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ND: no data; mTOR: mammalian target of rapamycin; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; PFS: progression-free survival; RCC: renal cell carcinoma; RCT: randomized controlled trial; AE: adverse event; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor					

Table 7: Characteristics of the intervention – RCT, indirect comparison: nivolumab vs. sunitinib (research questions 1 and 2)(multipage table)

Study	Intervention	Comparison
Cabozantinib + nivolumab vs. sunitinib		
CheckMate 9ER	Cabozantinib 40 mg/day, orally + nivolumab 240 mg IV every 2 weeks	Sunitinib 50 mg/day, orally duration of cycle: 6 weeks (4 weeks of treatment, followed by a 2-week rest period)
	Dose adjustments	
	Cabozantinib: treatment interruption or 2 dose reductions due to toxicity are allowed[a]: ▪ 20 mg/day and ▪ interval prolongations to 20 mg every second day nivolumab: no dose reduction allowed	Treatment interruption or 2 dose reductions due to toxicity allowed in 12.5 mg steps up to the minimum dose of 25 mg[a] dose escalations possible if a CYP3A4 inducer is required
	Permitted pretreatment ▪ for completely resectable RCC, adjuvant or neoadjuvant treatment not directed against VEGF or VEGF receptors if the recurrence occurred ≥ 6 months after completion of adjuvant or neoadjuvant treatment. **non-permitted pretreatment** ▪ VEGF-, MET-, AXL-, KIT- or RET-targeted therapy (e.g. sunitinib, pazopanib, axitinib, tivozanib, sorafenib, lenvatinib, bevacizumab, cabozantinib) ▪ antibodies against PD-1, PD-L1, PD-L2, CD137, CTLA-4 or other drugs aimed at T-cell co-stimulation or checkpoint signal pathways ▪ major surgeries < 6 weeks before randomization[b] ▪ radiotherapy ≤ 4 weeks before randomization (in case of bone lesions: ≤ 2 weeks before randomization) ▪ strong CYP3A4 inducers or CYP3A4 inhibitors ≤ 14 days before randomization ▪ systemic therapy with corticosteroids (> 10 mg/day prednisone equivalent) and other immunosuppressants ≤ 14 days before randomization **permitted concomitant treatment** ▪ low molecular weight heparin or aspirin (≤ 325 mg/day) ▪ premedication due to infusion-related reactions (caused by nivolumab) in the intervention arm (antihistamines, analgesics, corticosteroids) **non-permitted concomitant treatment** ▪ anticoagulants (warfarin or drugs similar to warfarin, thrombin or FXa inhibitors) in therapeutic doses	

Table 7: Characteristics of the intervention – RCT, indirect comparison: nivolumab vs. sunitinib (research questions 1 and 2)(multipage table)

Study	Intervention	Comparison
Pembrolizumab + axitinib vs. sunitinib		
KEYNOTE-426	Pembrolizumab 200 mg IV every 3 weeks + axitinib 5 mg orally, twice daily	Sunitinib 50 mg/day, orally duration of cycle: 6 weeks (4 weeks of treatment, followed by a 2-week rest period)
	Dose adjustments Pembrolizumab: ▪ no dose adjustment allowed ▪ treatment interruptions ≤ 12 weeks or treatment discontinuation due to toxicity allowed axitinib: ▪ if no AEs (CTCAE grade 2) occur, dose increase to 7 mg after 6 weeks and to 10 mg after another 6 weeks possible ▪ 2 dose reductions allowed[a] ▫ 3 mg twice daily ▫ 2 mg twice daily ▪ treatment interruptions ≤ 3 weeks[c] or treatment discontinuation due to toxicity allowed	▪ Treatment interruption or 2 dose reductions due to toxicity in 12.5 mg steps up to the minimum dose of 25 mg allowed[a], followed by re-escalation also in 12.5 mg steps; dose escalations possible if a CYP3A4 inducer is required
	Permitted pretreatment ▪ adjuvant or neoadjuvant treatment with VEGF/VEGFR or mTor-targeted drugs > 12 months before randomization **non-permitted pretreatment** ▪ antibodies against PD-1, PD-L1, PD-L2 or other immunoregulatory receptors/mechanisms ▪ systemic therapy for the advanced RCC or within the last 2 years in case of active autoimmune disorders ▪ major surgeries ≤ 4 weeks before randomization ▪ other investigational drugs ≤ 4 weeks before randomization ▪ radiotherapy: ≤ 2 weeks before randomization[d] ▪ immunosuppressants ≤ 7 days before randomization[e] ▪ strong CYP3A4/5 inhibitors or inducers ≤ 7 days before randomization **permitted concomitant treatment** ▪ premedication due to infusion-related reactions (caused by pembrolizumab) in the intervention arm (antihistamines, analgesics) ▪ **non-permitted concomitant treatment** ▪ therapies that were not allowed even as pretreatment ▪ any systemic anti-cancer treatment ▪ only sunitinib arm: antiarrhythmics ▪ only pembrolizumab + axitinib arm: systemic glucocorticoids (except for prophylactic therapy of allergic reactions and for the treatment of AEs)	

Table 7: Characteristics of the intervention – RCT, indirect comparison: nivolumab vs. sunitinib (research questions 1 and 2)(multipage table)

Study	Intervention	Comparison
a. A required further dose reduction resulted in a permanent discontinuation of the drug. b. Nephrectomy < 4 weeks before randomization. c. Prolonged treatment interruptions had to be agreed with the sponsor. d. Symptomatic radiation of individual lesions or the brain were allowed after consultation with the sponsor. e. Exception: in case of metastases in the CNS. AE: adverse event; AXL: growth arrest-specific 6 receptor; CD137: Tumor Necrosis Factor Receptor Superfamily Member 9; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; CYP3A4: cytochrome P450 3A4; I. v.: intravenous; KIT: Platelet Derived Growth Factor Receptor; MET: mesenchymal–epithelial transition factor; mTOR: mechanistic target of rapamycin; PD-1: programmed cell death protein1; PD-L1/PD-L2: programmed cell death ligand 1/2; RCC: renal cell carcinoma; RCT: randomized controlled trial; RET: rearranged during transfection (receptor tyrosine kinase); VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor		

Study CheckMate 9ER (study with cabozantinib + nivolumab)

The CheckMate 9ER study was a randomized, open-label, active-controlled approval study on the comparison of cabozantinib + nivolumab with sunitinib. The study included adults with advanced or metastatic RCC (stage IV according to the AJCC classification) with clear-cell component. Patients were not allowed to have received any prior systemic therapy for advanced disease; adjuvant or neoadjuvant therapy for completely resectable RCC was allowed if recurrence had occurred ≥ 6 months after the last dose of adjuvant or neoadjuvant therapy. The patients were to be in good general condition KPS ≥ 70%). Patients with RCC without a clear-cell component, with a KPS < 70% or with active brain metastases were excluded from participation in the study; hence, no data are available for them.

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

- favourable risk profile (IMDC score 0)
- intermediate risk profile (IMDC score 1-2)
- poor risk profile (IMDC score ≥ 3)

Overall, 651 patients were randomly allocated in a 1:1 ratio either to treatment with cabozantinib + nivolumab (N = 323) or to sunitinib (N = 328). Randomization was stratified according to IMDC risk profile (favourable vs. intermediate vs. poor), region (USA/Canada/Western Europe/Northern Europe vs. rest of the world) and PD-L1 status (≥ 1% vs. < 1% or undetermined).

Treatment with cabozantinib + nivolumab was in accordance with the regimen described in Table 7 and was in compliance with the recommendations provided in the Summary of Product Summary of Product Characteristics (SPC) [20-22].

The primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, symptoms, health status and AEs.

Patients were treated until disease progression, the occurrence of unacceptable, persistent toxicity or discontinuation of therapy at the decision of the physician or study participant. Treatment with nivolumab was limited to 2 years in the intervention arm.

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

After discontinuation of the study medication, there were no restrictions regarding subsequent therapies. The subsequent antineoplastic therapies used in the study are presented in Table 11.

Relevant subpopulation of the CheckMate 9ER study

The subpopulation of patients with favourable risk profile (IMDC score 0) of the CheckMate 9ER study is relevant for research question 1. These were 74 patients in the cabozantinib + nivolumab arm and 72 patients in the sunitinib arm. In Module 4 D, the company presented analyses for this subpopulation. These were used for the benefit assessment for research question 1.

Study KEYNOTE-426 (study with pembrolizumab + axitinib)

The KEYNOTE-426 study is a randomized, open-label, active-controlled approval study on the comparison of pembrolizumab + axitinib with sunitinib. The study included adults with advanced or metastatic clear-cell RCC (stage IV according to the AJCC classification). The patients were not allowed to have received any prior systemic therapy for advanced disease; any adjuvant or neoadjuvant therapy had to be completed 12 months before the start of the study. The patients were to be in good general condition (KPS ≥ 70%). Patients with non-clear cell RCC, with a KPS < 70 % or with active brain metastases were excluded from participation in the study; hence, no data are available for them.

The study included patients regardless of their risk profile. However, the IMDC score in the study was recorded as a disease characteristic at the beginning of the study so that it is possible to differentiate patients based on their risk profile according to the IMDC score.

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

Treatment with pembrolizumab + axitinib was in accordance with the regimen described in Table 7 and was in compliance with the recommendations provided in the SPCs [22-24].

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

Patients were treated until disease progression, the occurrence of unacceptable, persistent toxicity or discontinuation of therapy at the decision of the physician or study participant. Treatment in the intervention arm was restricted by the maximum number of allowed cycles (35 cycles) of pembrolizumab. At the time of the third data cut-off (6 January 2020), 19 (4.4% related to the pembrolizumab + nivolumab arm), patients had achieved this maximum treatment duration with pembrolizumab.

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

After discontinuation of the study medication, there were no restrictions regarding subsequent therapies. The subsequent antineoplastic therapies used in the study are presented in Table 11.

Relevant subpopulation of the KEYNOTE-426 study

The subpopulation of patients with favourable risk profile (IMDC score 0) of the KEYNOTE-426 study is relevant for research question 1. These were 138 patients in the pembrolizumab + axitinib arm and 131 patients in the sunitinib arm. In Module 4 D, the company presented analyses for this subpopulation. These were used for the benefit assessment for research question 1.

2.3.3.2 Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, total population

Study **outcome category** **outcome**	**Planned follow-up observation**
Cabozantinib + nivolumab vs. sunitinib	
CheckMate 9ER	
Mortality	
Overall survival	Until death, withdrawal of consent, lost to follow-up or end of study
Morbidity	
Symptoms (FKSI-DRS)	No follow-up after the last administration of the study medication
Health status (EQ-5D-3L VAS)	Until death, withdrawal of consent, lost to follow-up or end of study
Health-related quality of life	Outcome not recorded
Side effects	
All outcomes in the category of side effects	100 days after the last administration of the study medication[a]
Pembrolizumab + axitinib vs. sunitinib	
KEYNOTE -426	
Mortality	
Overall survival	Until death, withdrawal of consent or end of study
Morbidity	
Symptoms (EORTC QLQ-C30, FKSI-DRS)	Until 30 days after the last dose of the study medication
Health status (EQ-5D VAS)	Until 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30)	Until 30 days after the last dose of the study medication
Side effects	
AEs and severe AEs	Until 30 days after the last dose of the study medication
SAEs	Until 90 days after the last dose of the study medication or until 30 days after the last dose of the study medication if a new antineoplastic therapy is started

a. For the CheckMate 9ER study had, there are analyses with both 30-day and 100-day follow-up observation periods. In order to create a follow-up period comparable with the KEYNOTE 426 study, the analyses with the 30-day follow-up period for the outcomes AEs, discontinuation due to AEs and severe AEs are used in the indirect comparison.

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

In the studies, the observation periods for the outcomes on morbidity (except "health status" recorded with the EQ-5D in the CheckMate 9ER study), health-related quality of life (only recorded in the KEYNOTE-426 study) and side effects were systematically shortened because

they were only recorded for the time of treatment with the study medication (plus 100 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival.

2.3.3.3 Data cut-offs

Study CheckMate 9ER

The CheckMate 9ER study is still ongoing. So far, results on 2 data cut-offs are available:

- First data cut-off (30 March 2020): prespecified first interim analysis on overall survival after 165 events, as well as final analysis of the outcome "PFS"
- Second data cut-off (10 September 2020): prespecified, second interim analysis for overall survival after 211 deaths

In Module 4 D, the company presented analyses on the second data cut-off for the indirect comparison. This was used for the present benefit assessment.

Study KEYNOTE-426

The KEYNOTE-426 study is still ongoing. So far, results on 3 data cut-offs are available:

- first data cut-off (24 August 2018): pre-specified first interim analysis on reaching 305 events in the outcome "PFS" and after at least 7 months of follow-up observation of all patients after randomization
- second data cut-off (2 January 2019): data cut-off conducted post hoc upon request by the European Medicines Agency (EMA)
- third data cut-off (6 January 2020): pre-specified second interim analysis after 487 events of the outcome "PFS" and 74% of the final required events of the outcome "overall survival" (or 299 deaths) had been achieved

In Module 4 D, the company presented analyses on the third data cut-off on "overall survival" and on the second data cut-off on the outcomes of the category "side effects". The company takes the results on "overall survival" at the third data cut-off corresponding to the populations of the research questions from the Powles 2020 publication [8]. However, in this publication, there are no results on side effects corresponding to the populations of the research questions, which is why the company used the second data cut-off for the outcomes on side effects, which it took from the benefit assessment procedure of pembrolizumab + axitinib [3,17,18]. Also for the present benefit assessment, the third data cut-off was used for the outcome "overall survival", and the second data cut-off was used for the outcomes on side effects.

2.3.3.4 Similarity of the relevant subpopulations of the studies CheckMate 9ER and KEYNOTE-426 not assessable due to limited information

A key requirement for the consideration of studies in the adjusted indirect comparison is the evaluation of similarity [1,25,26]. According to the similarity assumption, the studies considered are comparable with regard to possible effect modifiers across all interventions. Potential effect modifiers (e.g. patient characteristics, study characteristics, intervention characteristics) (e.g. patient characteristics, study characteristics, intervention characteristics) as well as methodological factors (e.g. outcome characteristics) must be taken into account here [27].

The two studies CheckMate 9ER and KEYNOTE-426 are similar with regard to the study design. Both studies are multicentre, open-label RCTs that included adult patients with treatment-naive advanced or metastatic RCC. The administration of the common comparator sunitinib also only differed marginally between the two studies. Detailed information on the study design and the interventions in the two studies can be found in Section 2.3.3.1.

The company used the comparison of the patient characteristics on the basis of the total population of both studies and assessed them as similar. The company does not provide an explanation of the extent to which this results in a similarity for the patient population with a favourable risk profile.

The approach of the company was not appropriate. The two studies CheckMate 9ER and KEYNOTE-426 included patients regardless of their risk profile. The subpopulation of patients with favourable risk profile relevant to research question 1 only accounts for a small proportion of the total population in both studies, 22% (CheckMate 9ER) and 31% (KEYNOTE-426).

Information on the patient characteristics of the subpopulation relevant for research question 1 (favourable risk profile) is only available for the CheckMate 9ER study. Corresponding data are missing for KEYNOTE-426. Since, in contrast to the CheckMate 9ER study, there is no information on the subpopulation with an intermediate or poor risk profile for the KEYNOTE-426 study (research question 2), it cannot be deduced (also indirectly) with sufficient certainty that the subpopulation of the KEYNOTE-426 study is sufficiently similar to that of the CheckMate 9ER study.

Regardless of this and analogous to question 2, the indirect comparison between the two studies CheckMate 9ER and KEYNOTE-426 allowed no conclusions on the added benefit for the outcomes of the categories “morbidity”, “health-related quality of life” and “side effects”. There were no or no usable data on the outcomes of the categories “morbidity” and “health-related quality of life”. For the outcomes of the side effects category, the certainty of results of the indirect comparison is insufficient due to the high outcome-specific risk of bias in at least one of the studies. This means that even if the similarity between the two studies CheckMate 9ER and KEYNOTE-426 were assumed to be given for research question 1, only the outcome “overall survival” would be evaluable - as with research question 2. The consideration of the

results on the outcome "overall survival" for the relevant subpopulation of research question 1 (favourable risk profile) presented by the company in Module 4 D yields no statistically significant difference between cabozantinib + nivolumab and pembrolizumab + axitinib. The results are presented as supplementary information in Appendix C of the full dossier assessment.

2.3.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of cabozantinib + nivolumab in comparison with the ACT in adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0).

This resulted in no hint of an added benefit of cabozantinib + nivolumab in comparison with the ACT; an added benefit is therefore not proven.

2.3.5 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of cabozantinib + nivolumab versus the ACT in adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0), the added benefit of cabozantinib + nivolumab is not proven for these patients.

This assessment deviates from that of the company, which derived a hint of a non-quantifiable added benefit.

2.4 Research question 2: Adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)

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 cabozantinib + nivolumab (status: 6 March 2021)
- bibliographical literature search on cabozantinib + nivolumab (last search on 1 March 2021)
- search in trial registries/trial results databases for studies on cabozantinib + nivolumab (last search on 1 March 2021)
- search on the G-BA website for cabozantinib + nivolumab (last search on 9 March 2021)
- bibliographical literature search on the ACT (last search on 1 March 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 1 March 2021)
- search on the G-BA website for the ACT (last search on 9 March 2021)

To check the completeness of the study pool:

- search in trial registries for studies on cabozantinib + nivolumab (last search on 19 May 2021); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on the ACT (last search on 11 June 2021); for search strategies, see Appendix A of the full dossier assessment

Direct comparison

Concurring with the company, no relevant RCT on the direct comparison of cabozantinib + nivolumab versus the ACT was identified.

However, deviating from this approach, the company used the CheckMate 9ER study as direct comparator study of cabozantinib + nivolumab versus sunitinib for the derivation of the added benefit (see Section 2.2).

Indirect comparison

As the company identified no RCTs versus one of the ACTs specified by the G-BA, it searched for RCTs for an adjusted indirect comparison. In doing so, it first searched for RCTs with the intervention "nivolumab + cabozantinib" to be assessed and identified one relevant RCT on the comparison with sunitinib:

- CA209-9ER (CheckMate 9ER): cabozantinib + nivolumab vs. sunitinib [7]

For the indirect comparison, the company explained to conduct an information retrieval on studies with the ACT and the common comparator sunitinib. The restriction to sunitinib as a common comparator is appropriate, as the check of the completeness of the study pool identified no further relevant RCT with cabozantinib + nivolumab and thus no further relevant common comparator for a possible adjusted indirect comparison.

However, according to the tabular presentation of the inclusion and exclusion criteria and in contrast to the statement in its research question, the company did not select by studies for all options of the ACT, but limited the selection exclusively to studies with pembrolizumab + axitinib.

On the side of the ACT, the company identified the following study for pembrolizumab + axitinib:

- KEYNOTE 426: pembrolizumab + axitinib vs. sunitinib [8,9]

Concurring with the company, the check of the completeness of the study pool identified no relevant study on the comparison of pembrolizumab + axitinib vs. sunitinib.

2.4.2 Studies included

The studies CheckMate 9ER and KEYNOTE-426 are included in the benefit assessment on research question 2. The data on the studies included can be found in Section 2.3.2 and Table 5.

Figure 1 shows a schematic representation of the indirect comparison (Section 2.3.2).

2.4.3 Study characteristics

The information on the study characteristics of the studies CheckMate 9ER and KEYNOTE-426 can be found in Section 2.3.3 (Table 6 and Table 7).

2.4.3.1 Study design

Study CheckMate 9ER (study with cabozantinib + nivolumab)

The study CheckMate 9ER is presented and described in detail in Section 2.3.3.

Relevant subpopulation

The subpopulation of patients with intermediate or poor risk profile (IMDC score 1 to 6) of the CheckMate 9ER study is relevant for research question 2. This subpopulation comprised 249 patients in the cabozantinib + nivolumab arm and 256 patients in the sunitinib arm (see Table 6). The analyses of this subpopulation presented by the company were used for the benefit assessment for research question 2.

Study KEYNOTE-426 (study with pembrolizumab + axitinib)

The study KEYNOTE-426 is presented and described in detail in Section 2.3.3.

Relevant subpopulation

The subpopulation of patients with intermediate or poor risk profile (IMDC score 1 to 6) of the KEYNOTE-426 study is relevant for research question 2. This subpopulation comprised 294 patients in the pembrolizumab + axitinib arm and 298 patients in the sunitinib arm (see Table 6). The analyses of this subpopulation presented by the company were used for the benefit assessment for research question 2.

2.4.3.2 Planned duration of follow-up observation in the studies CheckMate 9ER and KEYNOTE-426

Data on the planned duration of follow-up observation of the patients for the individual outcomes in the studies CheckMate 9ER and KEYNOTE-426 can be found in Section 2.3.3.2 and Table 8.

2.4.3.3 Data cut-offs

The data cut-offs of the studies CheckMate 9ER and KEYNOTE-426 are presented in Section 2.3.3.3.

2.4.3.4 Patient characteristics

Table 9 shows the characteristics of the patients in the studies included for research question 2.

Table 9: Characteristics of the study population – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2 (multipage table)

Study characteristic category	CheckMate 9ER		KEYNOTE -426	
	cabozantinib + nivolumab	sunitinib	sunitinib	pembrolizumab + axitinib
	N[a] = 249	N[a] = 256	N[a] = 298	N[a] = 294
Age [years], mean (SD)	61 (10)	60 (11)	ND	ND
Sex [F/M], %	22/78	29/71	ND	ND
Family origin, n (%)				
White	202 (81.1)	205 (80.1)	ND	ND
Non-white	47 (18.9)[b]	50 (19.5)[b]	ND	ND
Not recorded	0 (0)	1 (0.4)	ND	ND
Geographical region, n (%)				
United States/Canada/Central Europe/Northern Europe (CheckMate 9ER) or North America/Western Europe (KEYNOTE-426)	119 (47.8)	124 (48.4)	ND	ND
Rest of the world	130 (52.2)	132 (51.6)	ND	ND
Karnofsky performance status, n (%)				
70	14 (5.6)	17 (6.6)	ND	ND
80	45 (18.1)	55 (21.5)		
90	86 (34.5)	92 (35.9)	ND	ND
100	104 (41.8)	91 (35.5)		
Not recorded	0 (0)	1 (0.4)	ND	ND
PD-L1 status[c], n (%)				
≥ 1 %	70 (28.1)	71 (27.7)	ND	ND
< 1% or undetermined	171 (68.7)	179 (69.9)	ND	ND
Not recorded	8 (3.2)	6 (2.3)	ND	ND
IMDC risk profile at baseline (IRT), n (%)				
IMDC score 0	0 (0)	0 (0)	ND	ND
IMDC score 1-2	188 (75.5)	188 (73.4)	ND	ND
IMDC score 3-6	61 (24.5)	68 (26.6)	ND	ND
Most common location of metastases, n (%)				
Lungs	184 (73.9)	202 (78.9)	ND	ND
Lymph nodes	103 (41.4)	104 (40.6)	ND	ND
Bone	58 (23.3)	65 (25.4)	ND	ND
Liver	62 (24.9)	46 (18.0)	ND	ND
Adrenal gland	24 (9.6)	28 (10.9)	ND	ND

Table 9: Characteristics of the study population – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2 (multipage table)

Study characteristic category	CheckMate 9ER		KEYNOTE -426	
	cabozantinib + nivolumab	sunitinib	sunitinib	pembrolizumab + axitinib
	N[a] = 249	N[a] = 256	N[a] = 298	N[a] = 294
Number of sites with at least 1 lesion, n (%)				
1	42 (16.9)	51 (19.9)	ND	ND
2	75 (30.1)	65 (25.4)	ND	ND
3	65 (26.1)	68 (26.6)	ND	ND
4	40 (16.1)	48 (18.8)	ND	ND
≥ 5	26 (10.4)	22 (8.6)	ND	ND
Previous nephrectomy, n (%)				
Yes	159 (63.9)	174 (68.0)	ND	ND
No	90 (36.1)	82 (32.0)	ND	ND
Previous radiotherapy, n (%)				
Yes	36 (14.5)	39 (15.2)	ND	ND
No	213 (85.5)	217 (84.8)	ND	ND
Sarcomatoid features, n (%)				
Yes	30 (12.0)	36 (14.1)	ND	ND
No	212 (85.1)	213 (83.2)	ND	ND
Not recorded	7 (2.8)	7 (2.7)	ND	ND
Treatment discontinuation, n (%)	ND	ND	ND	ND
Study discontinuation, n (%)	ND	ND	ND	ND

a. Number of randomized patients in the relevant subpopulation.
b. Institute's calculation.
c. Analytical method IHC; number of stained tumour cells among at least 100 evaluable tumour cells.

F: female; IHC: immunohistochemistry; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IRT: Interactive Response Technology; ND: no data; M: male; n: number of patients in the category; N: number of randomized patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; SD: standard deviation

Information on the patient characteristics of the subpopulation relevant for research question 2 (intermediate or poor risk profile) is only available for the CheckMate 9ER study in Module 4 D. Corresponding data are missing for KEYNOTE-426.

A comparative description of the study arms between the two studies is thus not possible for the subpopulation relevant for research question 2. However, the total populations of the studies mainly comprised patients with intermediate or poor risk profile (approx. 80% in the CheckMate 9ER study and approx. 70% in the KEYNOTE-426 study). The patient characteristics of the total populations of both studies are therefore presented in Table 22, Appendix B of the full benefit assessment.

Within the CheckMate 9ER study and related to the relevant subpopulation, the characteristics are sufficiently balanced between the two study arms. The mean age of the patient population was 61 years. There are slightly less women in the cabozantinib + nivolumab arm (22%) than in the sunitinib arm (29%). The disease-specific patient characteristics such as KPS, PD-L1 status, location of the metastases and number of sites with at least one lesion are largely comparable between the arms of CheckMate 9ER.

Related to the total population, the characteristics of the patients included in the KEYNOTE-426 study are comparable between the two study arms (see Table 22 in Appendix B of the full dossier assessment).

2.4.3.5 Treatment durations and observation periods

Information on treatment durations and observation periods are not available for the relevant subpopulation of research question 2. However, the total populations of the studies mainly comprised patients with intermediate or poor risk profile (approx. 80% in the CheckMate 9ER study and approx. 70% in the KEYNOTE-426 study). Therefore, Table 10 provides information on the patients' mean/median treatment duration and the mean/median observation period for individual outcomes for the total population of the studies CheckMate 9ER and KEYNOTE-426.

Table 10: Information on the course of the study – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, total population (multipage table)

Study **duration of the study phase** **outcome category**	**Intervention**	**Common comparator**
Cabozantinib + nivolumab vs. sunitinib	**Cabozantinib + nivolumab**	**Sunitinib**
CheckMate 9ER[a]		
Data cut-off 10 September 2020		
Treatment duration [months]		
Median [min; max]	17.99 [0.2; 32.2]	15.90 [0.5; 33.1]
Observation period [months]		
Overall survival		
Median [min; max]	20.50 [0.0; 32.9]	19.40 [0.0; 32.7]
Morbidity, side effects	ND	ND
Pembrolizumab + axitinib vs. sunitinib	**Pembrolizumab + axitinib**	**Sunitinib**
KEYNOTE 426[a]		
Data cut-off 2 January 2019		
Treatment duration [months]		
Median [min; max]	14.03 [0.03; 25.69]	10.42 [0.07; 25.76]
Median [Q1; Q3]	14.03 [6.90; 18.53]	10.42 [3.68; 15.61]
Mean (SD)	13.03 (6.94)	10.19 (6.99)
Observation period [months]		
Overall survival		
Median [min; max]	17.23 [ND]	15.51 [ND]
Morbidity	ND	ND
Health-related quality of life	ND	ND
Side effects (AEs)[b]		
Median [Q1; Q3]	14.13 [7.89; 18.89]	11.34 [4.67; 15.97]
Mean (SD)	13.44 (6.57)	10.93 (6.81)
Side effects (SAEs)[b]		
Median [Q1; Q3]	14.49 [9.56; 19.12]	12.19 [6.60; 16.69]
Mean (SD)	14.23 (6.05)	12.01 (6.36)
Data cut-off 06/01/2020		
Treatment duration [months]	ND	ND
Observation period [months]		
Overall survival, morbidity, health-related quality of life, side effects	ND[c]	ND[c]

Table 10: Information on the course of the study – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, total population (multipage table)

Study duration of the study phase outcome category	Intervention	Common comparator
a. It must be assumed that the data refer to all randomized patients, however, concrete information is not available. b. All subjects as treated (ASaT) population: 429 vs. 425 patients respectively in the intervention or common comparator arm. c. It can be learned from the Powles 2020 publication [8] that the median observation periods at this point in time accounted for 30.6 months considered together in both arms. An explanation for the large median difference of about 15 months between the second data cut-off (2 January 2019) and the third data cut-off (6 January 2020) is not apparent from the available data. AE: adverse event; ASaT: All Subjects as Treated; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation		

Between the treatment arms within the study CheckMate 9ER and within the study KEYNOTE-426, there are differences in the treatment and observation durations of the total population. The differences in the treatment durations and the observation periods for the AE outcomes (between the arms of a study) can be ascribed to differences in the treatment discontinuation rates chiefly due to disease progression.

Observation periods and treatment duration also differed between the studies. A description within the framework of the similarity examination can be found in Section 2.4.4.

2.4.3.6 Subsequent therapies

Results on subsequent antineoplastic therapies are not available for the relevant subpopulation of research question 2. Table 11 shows for the total populations of the CheckMate 9ER and KEYNOTE 426 studies which subsequent therapies patients received after having discontinued the study medication in relation to the total population.

Table 11: Information on subsequent antineoplastic therapies – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, total population

Study drug class	Patients with subsequent therapy n (%)	
	Intervention	**Comparison**
Cabozantinib + nivolumab vs. sunitinib		
CheckMate 9ER data cut-off 10 September 2020	**Cabozantinib + nivolumab** **N[a] = 323**	**Sunitinib** **N[a] = 328**
Total[b]	84 (26.0)	128 (39.0)
Subsequent systemic therapy	56 (17.3)	112 (34.1)
Immunotherapy (PD-1/PD-L1 inhibitors and/or CTLA-4 inhibitors)	20 (6.2)	95 (29.0)
PD-1/PD-L1 inhibitors	13 (4.0)	78 (23.8)
Angiogenesis inhibitors	44 (13.6)	48 (14.6)
Pembrolizumab + axitinib vs. sunitinib		
KEYNOTE-426 (data cut-off 6 January 2020)	**Pembrolizumab + axitinib** **N[a] = 432**	**Sunitinib** **N[a] = 429**
Total[b]	ND	ND
Subsequent systemic therapy	170 (39.4[c])	242 (56.4[c])
PD-1/PD-L1 inhibitors	25 (5.8[c])	169 (39.4[c])
VEGF/VEGFR inhibitors	153 (35.4[c])	159 (37.1[c])
Other[d]	47 (10.9[c])	54 (12.6[c])

a. Number of patients: intention to treat.
b. Including radiotherapy, surgery or systemic therapy; patients could have received > 1 subsequent therapy.
c. Institute's calculation.
d. Includes doxorubicin, everolimus, glutaminase inhibitor (unspecified), ibrutinib, interferon (unspecified), interferon alfa-2a, interferon gamma, investigational products (unspecified), ipilimumab, savolitinib, temsirolimus, vinblastine.

CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; n: number of patients with subsequent therapy; N: number of analysed patients; PD-(L)1: programmed cell death (ligand) 1; RCT: randomized controlled trial; VEGF(R): vascular endothelial growth factor (receptor)

Results on subsequent antineoplastic therapies are not available for the relevant subpopulation of research question 2.

However, the total populations of the studies mainly comprised patients with intermediate or poor risk profile (approx. 80% in the CheckMate 9ER study and approx. 70% in the KEYNOTE-426 study. Therefore, Table 11 shows information on the patients' subsequent therapies after discontinuation of the study medication in relation to the total population of the CheckMate 9ER and KEYNOTE 426 studies.

The data in Table 11 refer to subsequent therapies the patients received in the further course of disease. The data thus provide no information on which therapy the patients received as first subsequent therapy in each case. Therefore, hereinafter, statements can only be made as to

whether the subsequent therapies recommended in the guidelines were administered at any point in the further course of the disease.

For the checkpoint inhibitor-based therapy (cabozantinib + nivolumab) used in the intervention arm of the CheckMate 9ER study, the S3 guideline of the German Guideline Programme in Oncology [6] does not define which therapy should be used as standard subsequent therapy. In the CheckMate 9ER study, patients with subsequent therapy predominantly received angiogenesis inhibitors in the further course of the disease.

In the comparator arm of the CheckMate 9ER study with sunitinib monotherapy, 74% of the patients with subsequent therapies received immunotherapies (programmed cell death protein1 [PD-1)/programmed cell death ligand 1 [PD-L1] inhibitors and/or cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] inhibitors) as systemic therapy in the further course of the disease. The S3 guideline [6] recommends administration of the PD-1 checkpoint inhibitor nivolumab or the multikinase inhibitor cabozantinib as subsequent therapy. However, since only the drug classes and not the individual drugs are available for the current data cut-off, no final conclusion can be made as to the proportion of patients with nivolumab as subsequent therapy. However, data available on the first data cut-off [7] show that at this data cut-off almost 2 thirds of those who received subsequent systemic therapy received nivolumab as drug.

In the intervention arm of the KEYNOTE 426 study (pembrolizumab + axitinib), the patients with subsequent therapy mostly received vascular endothelial growth factor [VEGF]/vascular endothelial growth factor receptor [VEGFR] inhibitors as systemic therapy in the further course of the disease. The extent to which these include the tyrosine kinase inhibitors (TKIs) recommended in the S3 guideline [6] cannot be inferred from the available documents for the third data cut-off, as only information on the drug classes is available, but not on the individual drugs. However, from the data available on the second data cut-off it is clear that the patients largely received the TKIs cabozantinib or sunitinib at this time.

In the comparator arm of the KEYNOTE-426 study with a sunitinib monotherapy, PD-1/PD-L1 immune checkpoint inhibitor and VEGF/VEGFR inhibitors were applied as subsequent therapy. As described above, the S3 guideline [6] recommends administration of nivolumab or cabozantinib in this case. Here too, however, only data for the drug classes and not for the individual drugs are available for the third data cut-off. However, the data available on the second data cut-off make clear that the patients with subsequent therapy largely received nivolumab as subsequent systemic treatment.

2.4.4 Similarity of the studies CheckMate 9ER and KEYNOTE 426 for the indirect comparison (based on the total populations)

As described in the previous Section 2.4.3, information on the relevant subpopulation of research question 2 is only available for the CheckMate 9ER study, but not for KEYNOTE-426.

However, in the total populations of the studies, there are predominantly patients with intermediate or poor risk profile: approx. 80% in the CheckMate 9ER study and approx. 70% in the KEYNOTE 426 study. In view of this high proportion and taking into account the largely identical study design, it seems appropriate to carry out the following similarity test on the basis of the total populations.

Similarity of study conduct

Study design

Both included studies are multicentre, open-label RCTs that included adult patients with treatment-naive advanced or metastatic RCC. The IMDC score at baseline was recorded in both studies enabling a differentiation of the patients by risk profile according to the IMDC score within the studies.

Treatment duration and observation period

In both studies, treatment was performed until disease progression, unacceptable toxicity or treatment discontinuation following the decision by the physician or the patient. The administration of nivolumab in the CheckMate 9ER study was limited to 2 years and at the same time the administration of pembrolizumab in the KEYNOTE 426 study was limited to 35 cycles (i.e. 2 years) (see Table 7).

Observation of the outcome "overall survival" took place until death in both studies, the observation period for side effects was limited to 100 days in the CheckMate 9ER study and to 30 days (AEs, severe AEs, discontinuation due to AEs) or 90 days (SAEs) in KEYNOTE-426 (see Table 9).

Overall, the planned treatment durations and observation periods for "overall survival" and the outcomes on side effects are sufficiently similar.

Related to the total population of both studies (Table 10), the median treatment duration was 15.9 months in the common comparator arm (sunitinib) of the CheckMate 9ER study (second data cut-off at 10 September 2020) and 10.4 months in the KEYNOTE-246 study (second data cut-off at 2 January 2019). Thus, the ratio of the median treatment duration between the sunitinib arm with shorter treatment duration to the one with longer treatment is 65%. The median treatment duration in the CheckMate 9ER study is 5.5 months longer. However, for the present benefit assessment, the third data cut-off (6 January 2020) was used for "overall survival", for which Module 4 provides no information on the treatment duration. It can be assumed that at this later data cut-off of the KEYNOTE-426 study, treatment duration in the sunitinib arm was prolonged and thus approached the treatment duration of the CheckMate 9ER study.

Analogous to the treatment duration, the median observation time for the outcome "overall survival" in the common comparator arm (sunitinib) of the CheckMate 9ER study (19.4 months) (second data cut of 10 September 2020) differed by almost 4 months compared to the

KEYNOTE-426 study with 15.5 months (second data cut-off at 2 January 2019). The ratio between the arm with shorter treatment duration and the one with the longer treatment duration is 80%. Information for KEYNOTE-426 on the individual arms at the third data cut-off (6 January 2020) is missing here as well. It can be learned from the Powles 2020 publication [8] that the median observation periods at this point in time accounted for 30.6 months considered together in both arms. As with the treatment duration, it can also be assumed for the observation duration in the sunitinib arm to be prolonged at the later data cut-off in the KEYNOTE-426 study and to approach the observation duration of the CheckMate 9ER study.

The missing data on the treatment durations and observation periods both for the relevant subpopulation according to the research question and for the individual data cut-offs only permit a limited assessment of the similarity. However, based on the available information, it is assumed that the differences were largely acceptable, so that the similarity assumption is not rejected because of this.

Similarity of the patient population

Patient characteristics

Information on the patient characteristics for the relevant subpopulation of the present research question is only available for the CheckMate 9ER study (see Table 9). The examination of similarity was based on the total population (see Table 22 of the full dossier assessment).

The demographic and clinical characteristics of the patients included are comparable between the study arms of the two studies CheckMate 9ER and KEYNOTE-426.

The mean age of the patients was 60 to 61 years in both studies, and about one 80% were of white family origin. The gender ratio in both studies was similar, about one quarter of the patients were female.

Patient characteristics describing the disease severity are largely balanced between the patients regarding the KPS and the location of metastases. As far as the sarcomatoid features are concerned, a conclusive assessment is not possible as information is lacking for more than 30% in the KEYNOTE-426 study.

Pretreatment

Patients in both studies were allowed to have received an adjuvant or neoadjuvant therapy. However, there is no information on the number of patients who had actually received an adjuvant therapy. All patients were treatment-naive with regard to the advanced or metastatic stage. The proportion of patients who had previous nephrectomy was about 70% in the CheckMate 9ER study and thus slightly smaller than in the KEYNOTE-426 study (slightly above 80%). About 14% of the patients in the CheckMate 9ER study and slightly less than 10% in the KEYNOTE-426 study had received radiotherapy.

Subsequent therapies

Information on the subsequent therapies of the total population can be found in Table 11.

The data in Table 11 refer to subsequent therapies the patients received in the further course of disease. The data thus provide no information on which therapy the patients received as first subsequent therapy in each case. On the basis of the available data, only limited conclusions can be made about the similarity of the studies with regard to the subsequent therapies used.

In the sunitinib arm of CheckMate 9ER, 34% of the patients received a systemic therapy in the further course of the disease. In most cases, this systemic therapy was an immunotherapy consisting of PD-1/PD-L1 inhibitors and/or CTLA-4 inhibitors. The proportion with subsequent systemic therapy was higher in the KEYNOTE-426 study and amounted to 56% of the patients in the sunitinib arm. Thereby, equal proportions of patients received PD-1/PD-L1 and/or VEGF/VEGFR inhibitors in the further course of disease. As, in each case, information on the individual drugs is not available for the relevant data cut-off, it is difficult to assess whether these are the drugs cabozantinib or nivolumab recommended in the guidelines.

Similarity of the common comparator

With regard to dosage and possible dose reduction or interruption, administration of the common comparator sunitinib was comparable in both studies (see Table 7. For the common comparator sunitinib, there was thus sufficient similarity between the CheckMate 9ER study and the KeYNOTE-426 study.

Summary on the comparability of the studies

In the overall consideration, there are ambiguities or uncertainties regarding the similarity of the studies presented for the indirect comparison. These uncertainties are primarily due to the missing data for the relevant data cut-offs and for the populations according to research question 2 relevant for the present benefit assessment. However, these differences do not lead to a fundamental questioning of the similarity of the studies.

2.4.5 Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, total population

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			
Cabozantinib + nivolumab vs. sunitinib							
CheckMate 9ER	Yes	Yes	No	No	Yes	Yes	Low
Pembrolizumab + axitinib vs. sunitinib							
KEYNOTE -426	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low in both studies. This concurs with the company's assessment.

Limitations each resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.4.6.2.

Transferability to the German health care context

Study CheckMate 9ER

From the point of view of the company, the pre-specified inclusion and exclusion criteria, the characteristics of the interventions and the study population in the CheckMate 9ER study speak for a good transferability of the study results to the German health care context. The study population of CheckMate 9ER would completely cover the subpopulations relevant for the research questions. The study had included more than 80% of patients with white family origin. Moreover, the proportion of patients with a favourable risk profile according to IMDC was limited to about 25%, which would reflect the typical frequency of this group in metastatic RCC. From the point of view of the company, the dosage and the treatment algorithm in the study arms considered correspond to the specifications of the expert information relevant for Germany [20,22].

Study KEYNOTE-426

From the point of view of the company, the study population of the KEYNOTE-426 study, the patient characteristics and the study design speak for a good transferability of the study results to the German health care context. Patients included in the KEYNOTE-426 study were mostly of white family origin (> 79%). From the point of view of the company, the dosage and the treatment algorithm in the study arms considered correspond to the specifications of the SPCs relevant for Germany [22,23].

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.6 Results on added benefit

2.4.6.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Symptoms (Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease related Symptoms [FKSI-DRS])
  - Symptoms (EORTC QLQ-C30 symptom scale)
  - Health status (EQ-5D VAS)
- Health-related quality of life
  - Health-related quality of life (EORTC QLQ-C30 functional scale)
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Immune-related SAEs
  - Immune-related severe AEs (CTCAE grade ≥ 3)
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes of the category of morbidity in the dossier (Module 4 D).

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2

Study	Outcomes										
	Overall survival	Symptoms (FKSI-DRS)	Symptoms (EORTC-QLQ-C30[a])	Health status (EQ-5D-3L VAS)	Health-related quality of life (EORTC QLQ-C30[b])	SAEs	Severe AEs[c]	Discontinuation due to AEs	Immune-related SAEs[d]	Immune-related severe AEs[c, d]	Further specific AEs
Cabozantinib + nivolumab vs. sunitinib											
CheckMate 9ER	yes	yes	no[e]	yes	no[e]	Yes[f]	Yes[f]	Yes[f]	No[g]	No[g]	No[h]
Pembrolizumab + axitinib vs. sunitinib											
KEYNOTE-426	yes	No[i]	No[i]	No[i]	No[i]	Yes[j]	Yes[j]	Yes[j]	No[k]	No[k]	No[l]
Indirect comparison possible	Yes	No[m]	No[m]	No[m]	No[m]	No[n]	No[n]	No[n]	No[m]	No[m]	No[m]

a. Measured with the EORTC QLQ-C30 symptom scales.
b. Measured with the functional scales and the global health status of the EORTC QLQ-C30.
c. Severe AEs are operationalized as CTCAE grade ≥ 3.
d. In both studies, the recording of immune-related AEs was pre-specified and based on a continuously updated PT list.
e. Outcome not recorded.
f. Without recording of PTs which are related to the underlying disease, i.e. "progression of malignant neoplasms", "metastases in the CNS" and „bone metastases".
g. Results are only available for the individual immune-related AEs; however, total rates on the immune-related SAEs and immune-related severe AEs are not available.
h. Due to missing data on the relevant subpopulation for the KEYNOTE-426 study, further specific AEs were not chosen for the CheckMate 9ER study.
i. No usable data available due to unequal documentation times in the study arms; due to the staggered recording of the PROs, the burden of the treatment during the course of the cycle is unequally represented in the study arms.
j. Without recording of PTs which are related to the underlying disease, i.e. "progression of neoplasms", "progression of malignant neoplasms" and "disease progression".
k. Results corresponding to the populations of the research questions relevant for the present benefit assessment are not available.
l. No usable analyses available for the relevant subpopulation of the research questions on AEs relevant for the present benefit assessment; therefore, a selection of specific AEs was impossible.
m. There are no results suitable for the indirect comparison.
n. Requirement for the certainty of results to perform an adjusted indirect comparison was not met (see Table 14 and Section 2.4.6.2).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-3L: European Quality of Life-5 Dimensions 3 Levels; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Usable data on the PROs were not available for the KEYNOTE-426 study. In each case, this was due to unequal documentation times in the study arms. Due to this staggered recording of PROs, the burden of treatment over the course of the cycle is unequally represented in the study arms.

In the pembrolizumab + axitinib arm of the KEYNOTE-426 study, pembrolizumab was administered once at the beginning of a 3-week cycle and axitinib was administered continuously (see Table 7). PROs were recorded on day 1 of each cycle for the first 24 weeks of the study, i.e. every 3 weeks.

In the comparator arm, sunitinib was continuously administered for 4 weeks of a 6-week cycle, followed by a 2 weeks off therapy (see Table 7). In the first 24 weeks of the study, PROs were recorded on day 1 of a cycle and, after 4 weeks, additionally on day 29 of the respective cycle.

After week 24, PROs were recorded in parallel every 6 weeks at the start of a new cycle in both study arms (or at the start of every second cycle in the pembrolizumab + axitinib arm).

Due to this described staggered recording of PROs in the first 24 study weeks, the burden of treatment over the course of the cycle is unequally represented in the study arms. For example, in the sunitinib arm, patients are expected to experience a high burden of treatment immediately after the 4-week treatment phase. In contrast, the PROs in the pembrolizumab + axitinib arm were collected at the beginning of each new cycle. In contrast to the intervention arm, in the comparator arm, data collected at a point in time with a potentially high burden of treatment were taken into account in addition to the data collected at the beginning of the cycle, possibly resulting in an advantage in favour of the intervention. Due to the unequally presented courses of treatment in the study arms, the results of the PROs (measured using the EORTC-QLQ-C30, FKSI-DRS and EQ-5D VAS) provide no usable data and are thus not used for the assessment.

Since no usable data on the PROs are available for the KEYNOTE 426 study, an adjusted indirect comparison is not possible for the outcomes “symptoms” (assessed with the FKSI-DRS) and “health status” (assessed with the EQ-5D VAS).

2.4.6.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2

Study	Study level	Outcomes										
		Overall survival	Symptoms (FKSI-DRS)	Symptoms (EORTC-QLQ-C30[a])	Health status (EQ-5D-3L VAS)	Health-related quality of life (EORTC QLQ-C30[b])	SAEs[c]	Severe AEs[c, d]	Discontinuation due to AEs	Immune-related SAEs	Immune-related severe AEs[d]	Further specific AEs
Cabozantinib + nivolumab vs. sunitinib												
CheckMate 9ER	N	N	–[e]	–[e]	–[e]	–[e]	H[f]	H[f]	H[g]	–[e]	–[e]	–[h]
Pembrolizumab + axitinib vs. sunitinib												
KEYNOTE -426	N	N	–[e]	–[e]	–[e]	–[e]	H[f]	H[f]	H[g]	–[e]	–[e]	–[e]

a. Measured with the EORTC QLQ-C30 symptom scales.
b. Measured with the functional scales and the global health status of the EORTC QLQ-C30.
c: Without events caused by progression of the underlying disease.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. No (usable) data available for the indirect comparison; see Table 13 for reasons.
f. Incomplete observations for potentially informative reasons.
g. Lack of blinding in subjective decision for discontinuation.
h. Due to missing data on the relevant subpopulation for KEYNOTE-426, further specific AEs were not chosen for CheckMate 9ER.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D-3L: European Quality of Life-5 Dimensions 3 Levels; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

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

No or no usable data were available for the outcomes of symptoms (recorded with the FKSI-DRS and the EORTC QLQ-C30 symptom scale), of health status (measured with the EQ-5D VAS) and of health-related quality of life (recorded with the EORTC QLQ-C30 functional scale) (see Table 13). Therefore, the risk of bias was not assessed for these outcomes. This is consistent with the assessment of the company in that it also does not use the PROs collected using the EQ-5D VAS, FKSI-DRS and EORTC-CLQ-C30 for the indirect comparison without, however, justifying its approach.

Likewise, the risk of bias for the superordinate outcomes of immune-related SAEs and immune-related severe AEs as well as for other specific AE outcomes was not assessed, as no usable data were available here either. The company did not include immune-related SAEs, immune-related severe AEs and other specific AEs in its assessment for the indirect comparison. Consequently, the company did not assess the risk of bias for these two outcomes.

The risk of bias of the results on the outcome "discontinuation due to AEs" was rated as high due to the open-label study design. The risk of bias of each of the results on the superordinate outcome "severe AEs" and "SAEs" is high due to incomplete observations for potentially informative reasons. Frequency data on the reasons for treatment discontinuation are not available in both studies separately for the relevant subpopulations according to the questions and for KEYNOTE 426 also not for the data cut used. There is also a lack of information for both studies on the observation durations of the outcomes in the treatment arms separated by the questions for the data cut-offs used. The assessment of these risks of bias of the results concurs with the assessment of the company.

Results that show a high risk of bias in one of the two studies do not provide the certainty of results necessary to conduct an adjusted indirect comparison. Thus, there is no sufficient certainty of results for an adjusted indirect comparison for any of the outcomes of the side effects category for which usable data are available in the individual studies. Data for the present assessment that allow a meaningful adjusted indirect comparison are only available for overall survival. This is not consistent with the approach of the company, which, in addition to the outcome "overall survival", also used the outcomes "AEs", "SAEs", "discontinuation due to AEs" and "severe AEs" for an adjusted indirect comparison.

2.4.6.3 Results

Table 15 summarizes the results for the comparison of cabozantinib + nivolumab with pembrolizumab + axitinib in patients with treatment-naive advanced RCC. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Kaplan-Meier curves on the used event time analyses can be found in Appendix D of the full dossier assessment. Effect estimates on the outcomes "SAEs", "discontinuation due to AEs" and "severe AEs (CTCAE grade ≥ 3)" presented as supplementary information are found in Table 24 of the full dossier assessment.

Table 15: Results (mortality, morbidity, side effects) – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2 (multipage table)

Outcome category outcome comparison Study	Cabozantinib + nivolumab or pembrolizumab + axitinib		Sunitinib		Group difference
	N	median time to event in months [95% CI][a] patients with event n (%)	N	median time to event in months [95% CI][a] patients with event n (%)	HR [95% CI][b]; p-value[c]
Mortality					
Overall survival					
Cabozantinib + nivolumab vs. sunitinib					
CheckMate 9ER (data cut-off 10 September 2020)	249[d]	NA 71 (28.5)	256[d]	29.47 [23.82; NC] 101 (39.5)	0.62 [0.45; 0.84]; 0.002
Pembrolizumab + axitinib vs. sunitinib					
KEYNOTE-426 (data cut-off 6 January 2020)	294[d]	ND 116 (39.5)	298[d]	ND 154 (51.7)	0.63 [0.50; 0.81]; < 0.001
Indirect comparison using common comparators[e]:					
Cabozantinib + nivolumab vs. pembrolizumab + axitinib					0.98 [0.66; 1.46]
Morbidity					
Symptoms (FKSI-DRS)	No usable data[f]				
Symptoms (EORTC QLQ-C30)	Only recorded in KEYNOTE-426				
Health status (EQ-5D VAS)	No usable data[f]				
Health-related quality of life					
Health-related quality of life (EORTC QLQ-C30)	Only recorded in KEYNOTE-426				
Side effects					
AEs[g] (supplementary presentation)					
Follow-up: 30 days					
Cabozantinib + nivolumab vs. sunitinib					
CheckMate 9ER (data cut-off 10 September 2020)	246	0.46 [0.43; 0.49] 245 (99.6)	249	0.36 [0.33; 0.43] 246 (98.8)	–
Pembrolizumab + axitinib vs. sunitinib					
KEYNOTE-426 (data cut-off 2 January 2019)	292	ND 286 (97.9)	295	ND 295 (100)	–

Table 15: Results (mortality, morbidity, side effects) – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2 (multipage table)

Outcome category outcome comparison Study	Cabozantinib + nivolumab or pembrolizumab + axitinib		Sunitinib		Group difference
	N	median time to event in months [95% CI][a] patients with event n (%)	N	median time to event in months [95% CI][a] patients with event n (%)	HR [95% CI][b]; p-value[c]
SAEs[g]					
Follow-up: 100 days or 90 days					
Cabozantinib + nivolumab vs. sunitinib					
Checkmate 9ER (data cut-off 10 September 2020)	246	16.82 [12.22; 23.66] 124 (50.4)	249	19.25 [11.20; NA] 110 (44.2)	0.89 [0.69; 1.16]; 0.401
Pembrolizumab + axitinib vs. sunitinib					
KEYNOTE-426 (data cut-off 2 January 2019)	292	ND 136 (46.6)	295	ND 116 (39.3)	1.08 [0.84; 1.39] ND
Indirect comparison using common comparators[e]:					
Cabozantinib + nivolumab vs. pembrolizumab + axitinib					–[h]
Severe AEs[g,i]					
Follow-up: 30 days					
Cabozantinib + nivolumab vs. sunitinib					
CheckMate 9ER (data cut-off 10 September 2020)	246	4.37 [2.79; 5.78] 190 (77.2)	249	2.76 [2.10; 4.40] 176 (70.7)	0.86 [0.70; 1.06]; 0.177
Pembrolizumab + axitinib vs. sunitinib					
KEYNOTE-426 (data cut-off 2 January 2019)	292	ND 228 (78.1)	295	ND 220 (74.6)	0.90 [0.75; 1.08] ND
Indirect comparison using common comparators[e]:					
Cabozantinib + nivolumab vs. pembrolizumab + axitinib					–[h]
Discontinuation due to AEs[g]					
Follow-up: 30 days					
Cabozantinib + nivolumab vs. sunitinib					
Checkmate 9ER (data cut-off 10 September 2020)	246	NA 74 (30.1)	249	NA 41 (16.5)	1.46 [0.99; 2.15]; 0.054
Pembrolizumab + axitinib vs. sunitinib					
KEYNOTE-426 (data cut-off 2 January 2019)	292	ND 87 (29.8)	295	ND 44 (14.9)	1.82 [1.26; 2.63] ND
Indirect comparison using common comparators[e]:					
Cabozantinib + nivolumab vs. pembrolizumab + axitinib					–[h]
Immune-related SAEs	No usable data[f]				
Immune-related severe AEs	No usable data[f]				

Table 15: Results (mortality, morbidity, side effects) – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2 (multipage table)

Outcome category outcome comparison Study	Cabozantinib + nivolumab or pembrolizumab + axitinib		Sunitinib		Group difference
	N	median time to event in months [95% CI][a] patients with event n (%)	N	median time to event in months [95% CI][a] patients with event n (%)	HR [95% CI][b]; p-value[c]
a. Median and 95% CI: unstratified product limit estimate in the CheckMate 9ER study. b. HR and 95% CI: Cox proportional hazards model in the CheckMate 9ER study stratified by IMDC prognostic risk score (1–2, 3–6), PD-L1 tumour expression (≥ 1%, < 1% or undetermined) and region (USA/Canada/Western Europe/Northern Europe, rest of the world) according to IRT. c. In the CheckMate 9ER study calculated using the log-rank test, stratified by IMDC prognosis risk score (1-2, 3-6), PD-L1 tumour expression (≥ 1%, < 1% or undetermined) and region (USA/Canada/Western Europe/Northern Europe, rest of the world) according to IRT; in the KEYNOTE 426 study calculated using the Wald test. d. Number of randomized patients in the subpopulation according to research question 2. e. Indirect comparison according to Bucher [28]. f. See Table 13 for reasons. g. Without recording of the progression of the underlying disease (see Table 13). h. No presentation of effect estimations, as no hint, e.g. of an added benefit, is derived due to the outcome-specific high risk of bias in at least one of the studies of the indirect comparison and the resulting insufficient certainty of results of the indirect comparison (see Section 2.4.6.2). i. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IRT: Interactive Response Technology; N: number of patients who had received as least one dose of the study medication; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale				

There was one RCT on each side of the available adjusted indirect comparison. Hence, a check of the homogeneity assumption was not required. As there was no study of direct comparison of cabozantinib + nivolumab versus the pembrolizumab + axitinib, the consistency assumption could not be checked. Therefore, the adjusted indirect comparisons had at most a low certainty of results. Hence, at most hints, e.g. of an added benefit, can be derived based on the data available from the adjusted indirect comparison.

Moreover, the risk of bias of the results on the outcomes of the category “side effects” was rated as high in the studies CheckMate 9ER and KEYNOTE 426. The certainty of results of the results from the indirect comparisons is therefore not sufficient. Therefore, no indirect comparison was performed for these outcomes, and no hint of an added benefit was derived.

This assessment does not concur with that of the company, which conducted indirect comparisons for all outcomes of the category "side effects" considered by it.

Mortality

Overall survival

The adjusted indirect comparison showed no statistically significant difference between the treatment groups for the outcome "overall survival". Hence, there was no hint of an added benefit of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; an added benefit is therefore not proven.

This deviates from the company's assessment, which derived a hint of a non-quantifiable added benefit on the basis of the direct comparisons versus sunitinib.

Morbidity

The studies CheckMate 9ER and KEYNOTE-426 provide no usable data on the outcomes of the category "morbidity". Hence, there was no hint of an added benefit of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; an added benefit is therefore not proven.

This concurs with the company insofar as the company also described that no usable data were available for the indirect comparison on health status (recorded with the EQ-5D VAS) and symptoms (recorded with the FKSI-DRS). However, it assigned the instruments EQ/5D/VAS and FSKI-DRS to health-related quality of life.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the CheckMate 9ER study. Therefore, an adjusted indirect comparison is no possible. Hence, there was no hint of an added benefit of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; an added benefit is therefore not proven.

The company assigned the instruments EQ-5D-3L index, EQ-5D VAS, FKSI-19 and FSKI-DRS to health-related quality of life and described that no suitable data for an indirect comparison were available for the relevant subpopulation. However, on the basis of the CheckMate 9ER study, the company derived a non-quantifiable added benefit for the outcome "health-related quality of life" for the direct comparison of cabozantinib + nivolumab versus sunitinib.

Side effects

Due to insufficient certainty of results in both studies, an indirect comparison was not possible for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs". There were no usable data for the outcomes "immune-related SAEs" and "immune-related severe AEs" (CTCAE grade ≥ 3). This resulted in no hint of greater or lesser harm from

cabozantinib + nivolumab in comparison with pembrolizumab + axitinib; greater or lesser harm is therefore not proven.

This is consistent with the assessment of the company in that it also derived no greater or lesser harm for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs" on the basis of the indirect comparison. However, based on the CheckMate 9ER study, it derived non-quantifiable lesser harm for several specific AEs for the direct comparison of cabozantinib + nivolumab versus sunitinib, but not for the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "discontinuation due to AEs".

2.4.6.4 Subgroups and other effect modifiers

For the present benefit assessment of cabozantinib + nivolumab, only subgroup analyses for the subgroup characteristic "disease severity according to the IMDC score" are available for the indirect comparison. Consequently, the following subgroup characteristic pre-specified in the studies CheckMate 9ER and KEYNOTE 426 was considered in the benefit assessment.

- Risk profile (intermediate [IMDC score 1-2] vs. poor [IMDC score 3-6])

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

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

In the dossier, the company did not state whether there was an effect modification with a statistically significant interaction with the subgroup characteristic "risk profile". However, the company presented results of the subgroups. This resulted in no statistically significant difference between cabozantinib + nivolumab and pembrolizumab + axitinib. The Institute's calculation revealed no statistically significant interaction.

2.4.7 Probability and extent of added benefit

The derivation of probability and extent of added benefit for research question 2 at outcome level is shown below 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.

2.4.7.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.6 (see Table 16).

Table 16: Extent of the added benefit at outcome level: cabozantinib + nivolumab vs. pembrolizumab + axitinib, research question 2

Outcome category **outcome**	**Cabozantinib + nivolumab vs. pembrolizumab + axitinib** **median time to event (months)** **effect estimation [95% CI]; p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. ND 0.98 [0.66; 1.46]; ND	Lesser benefit/added benefit not proven
Morbidity		
Symptoms (FKSI-DRS)	No usable data[c]	Lesser benefit/added benefit not proven
Symptoms (EORTC QLQ-C30)	No data[d]	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
Health-related quality of life (EORTC QLQ-C30)	No data[d]	Lesser benefit/added benefit not proven
Side effects		
SAEs	No usable data[e]	Greater/lesser harm not proven
Severe AEs	No usable data[e]	Greater/lesser harm not proven
Discontinuation due to AEs	No usable data[e]	Greater/lesser harm not proven
Immune-related SAEs	No usable data[e]	Greater/lesser harm not proven
Immune-related severe AEs	No usable data[e]	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Unequal documentation times in the study arms within a study.
d. This outcome was not recorded in the CheckMate 9ER study.
d. No indirect comparison for the derivation is used due to an insufficient certainty of results (see Section 2.4.6.2).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; FKSI-DRS: Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; HR: hazard ratio; NA: not achieved; ND: no data; QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event; VAS: visual analogue scale

2.4.7.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of cabozantinib + nivolumab in comparison with pembrolizumab + nivolumab, research question 2

Positive effects	Negative effects
–	–
No (usable) data are available for each of the outcomes on morbidity, health-related quality of life and side effects.	

Overall, based on the adjusted indirect comparison using the common comparator sunitinib, there are neither positive nor negative effects of cabozantinib + nivolumab in comparison with pembrolizumab + axitinib for research question 2.

However, it should be noted that usable results with sufficient certainty of results for an indirect comparison are only available for the outcome "overall survival". There is no hint of an added benefit of cabozantinib + nivolumab for this outcome, as the indirect comparison showed no statistically significant difference. There were no or no usable data or the outcomes of the outcome categories "morbidity" and "health-related quality of life". No usable data for an indirect comparison are available for the outcome category of side effects, as the certainty of results was not sufficient for an indirect comparison. An adequate balancing of benefit and harm is impossible due to the lack of usable results on these outcome categories.

In summary, there was no hint of an added benefit of cabozantinib + nivolumab versus pembrolizumab + axitinib for adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1 to 2) or poor risk profile (IMDC score ≥ 3).

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of cabozantinib + nivolumab in comparison with the ACT is summarized in Table 18.

Table 18:Cabozantinib + nivolumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with treatment-naive advanced RCC with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven[c]
2	Adult patients with treatment-naive advanced RCC with intermediate (IMDC score 1-2) or poor risk profile (IMDC score ≥ 3)[b]	Pembrolizumab in combination with axitinib ▪ avelumab in combination with axitinib (only for patients with poor risk profile) or ▪ nivolumab in combination with ipilimumab or ▪ **pembrolizumab in combination with axitinib**	Added benefit not proven[c]

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 G-BA pointed out that the two risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Before this background, subgroup analyses for patients with intermediate and poor risk profiles were to be presented in the dossier.
c. The studies CheckMate 9ER and KEYNOTE-426 only included patients with RCC with clear-cell component and a Karnofsky performance status ≥ 70%. It remains unclear whether the observed effects can be transferred to patients without clear-cell component and a Karnofsky performance status < 70 %.

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

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

References for English extract

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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinie, Kombination mit Axitinib) [online]. 2020 [Accessed: 04.06.2021]. URL: https://www.g-ba.de/downloads/39-261-4289/2020-05-14_AM-RL-XII_Pembrolizumab-RCC_D-502_BAnz.pdf.

4. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Avelumab (neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinie, Kombination mit Axitinib) [online]. 2020 [Accessed: 08.07.2021]. URL: https://www.g-ba.de/downloads/39-261-4288/2020-05-14_AM-RL_XII_Avelumab_D-504_BAnz.pdf.

5. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Nivolumab (neues Anwendungsgebiet: Nierenzellkarzinom, in Kombination mit Ipilimumab, Erstlinienbehandlung) [online]. 2019 [Accessed: 08.07.2021]. URL: https://www.g-ba.de/downloads/39-261-3923/2019-08-15_AM-RL-XII_Nivolumab_D-439_BAnz.pdf.

6. Leitlinienprogramm Onkologie. Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms, Langversion 2.0, AWMF Registernummer: 043/017OL [online]. 2020 [Accessed: 29.06.2021]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Nierenzellkarzinom/Version_2/LL_Nierenzellkarzinom_Langversion_2.0.pdf.

7. Choueiri TK, Powles T, Burotto M et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2021; 384(9): 829-841. https://dx.doi.org/10.1056/NEJMoa2026982.

8. Powles T, Plimack ER, Soulieres D et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol 2020; 21(12): 1563-1573. https://dx.doi.org/10.1016/S1470-2045(20)30436-8.

9. Rini BI, Plimack ER, Stus V et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019; 380(12): 1116-1127. https://dx.doi.org/10.1056/NEJMoa1816714.

10. Bristol-Myers Squibb. A Study of Nivolumab Combined With Cabozantinib Compared to Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 9ER) [online]. 2021 [Accessed: 25.05.2021]. URL: https://ClinicalTrials.gov/show/NCT03141177.

11. Bristol-Myers Squibb International. A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma [online]. [Accessed: 25.05.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000759-20.

12. Ono Pharmaceutical. A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib Versus Sunitinib in Participants with Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma (ONO-4538-81/CA2099ER) [online]. 2021 [Accessed: 25.05.2021]. URL: https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-184076.

13. Merck Sharp & Dohme. A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426) [online]. [Accessed: 21.05.2021]. URL: https://www.pharmnet-bund.de/dynamic/de/arzneimittel-informationssystem/index.html.

14. Merck Sharp & Dohme. Study to Evaluate the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Axitinib Versus Sunitinib Monotherapy in Participants With Renal Cell Carcinoma (MK-3475-426/KEYNOTE-426) [online]. 2020 [Accessed: 18.06.2021]. URL: https://ClinicalTrials.gov/show/NCT02853331.

15. Merck Sharp & Dohme. A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426) [online]. [Accessed: 18.06.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000588-17.

16. Merck Sharp & Dohme. Eine randomisierte, offene Phase III Studie zur Beurteilung der Wirksamkeit und Sicherheit von Pembrolizumab (MK-3475) in Kombination mit Axitinib im Vergleich zu einer Monotherapie mit Sunitinib als Erstlinienbehandlung bei lokal fortgeschrittenem oder metastasiertem Nierenzellkarzinom (mRCC) (KEYNOTE-426) [online]. [Accessed: 18.06.2021]. URL: http://www.drks.de/DRKS00011432.

17. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pembrolizumab (neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinie, Kombination mit Axitinib) [online]. 2020 [Accessed: 04.06.2021]. URL: https://www.g-ba.de/downloads/40-268-6565/2020-05-14_AM-RL-XII_Pembrolizumab-RCC_D-502_TrG.pdf.

18. MSD Sharp & Dohme. Pembrolizumab (KEYTRUDA); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2019 [Accessed: 12.03.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/511/#dossier.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Nierenzellkarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 02.03.2020]. URL: https://www.iqwig.de/download/A19-99_Pembrolizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

20. Ipsen Pharma. Cabometyx 20mg/40 mg/60 mg Filmtabletten [online]. 2021 [Accessed: 14.06.2021]. URL: https://www.fachinfo.de/.

21. Bristol-Myers Squibb. Opdivo 10 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 14.06.2021]. URL: https://www.fachinfo.de/.

22. Pfizer. Sutent 12,5/25/37,5/50 mg Hartkapseln [online]. 2020 [Accessed: 14.06.2021]. URL: https://www.fachinfo.de/.

23. MSD Sharp & Dohme. Keytruda 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 17.06.2021]. URL: https://www.fachinfo.de/.

24. Pfizer. Inlyta 1/ 3/ 5/ 7 mg Filmtabletten [online]. 2020 [Accessed: 17.06.2021]. URL: https://www.fachinfo.de/.

25. Kiefer C, Sturtz S, Bender R. A simulation study to compare different estimation approaches for network meta-analysis and corresponding methods to evaluate the consistency assumption. BMC Med Res Methodol 2020; 20(1): 36. https://dx.doi.org/10.1186/s12874-020-0917-3.

26. Song F, Loke YK, Walsh T et al. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ 2009; 338: b1147. https://dx.doi.org/10.1136/bmj.b1147.

27. Cope S, Zhang J, Saletan S et al. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy versus chemotherapy for advanced breast cancer. BMC Med 2014; 12: 93. https://dx.doi.org/10.1186/1741-7015-12-93.

28. Bucher HC, Guyatt GH, Griffith LE et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691. https://dx.doi.org/10.1016/s0895-4356(97)00049-8.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-49.html.