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Nivolumab (renal cell carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Nivolumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; 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.

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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.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug nivolumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 3 May 2021.

Research question

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

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 nivolumab + cabozantinib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with treatment-naive advanced renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib
2	Adult patients with treatment-naive advanced renal cell carcinoma 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.
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 named the options specified by the G-BA, but additionally listed sunitinib and pazopanib as recommended treatment options, whereby it considered sunitinib to be particularly relevant. This deviation is not appropriate. The company did not cite any sources that adequately justify the additional consideration of sunitinib and pazopanib in the framework of the ACT. 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 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.

Study pool of the company

Direct comparison

No randomized controlled trial (RCT) of direct comparison was identified for the assessment of the added benefit of nivolumab + cabozantinib versus the ACT specified by the G-BA.

Indirect comparison

The company presented a total of 3 adjusted indirect comparisons across research questions on the common comparator sunitinib, each with the study CA209-9ER (CheckMate 9ER) on the side of the intervention. On the side of the ACT, the company considered the following study separately for each treatment option:

- KEYNOTE-426 (MK-3475-426): pembrolizumab + axitinib vs. sunitinib
- CA209-214 (CheckMate 214): nivolumab + ipilimumab vs. sunitinib
- JAVELIN Renal 101: avelumab + axitinib vs. sunitinib

In doing so, it considered different patient populations depending on the treatment option:

a) Nivolumab + cabozantinib versus pembrolizumab + axitinib: patients with any risk profile
b) Nivolumab + cabozantinib versus nivolumab + ipilimumab: patients with intermediate or poor risk profile
c) Nivolumab + cabozantinib versus avelumab + axitinib: patients with poor risk profile

The company presented the results obtained from these 3 indirect comparisons for the respective patient population under consideration. The company did not allocate the results to the separate research questions 1 (favourable risk profile) and 2 (intermediate or poor risk profile).

The unadjusted indirect comparison presented by the company are unsuitable for the present benefit assessment

Research question 1: patients with favourable risk profile (International Metastatic Renal Cell Carcinoma Database Consortium [IMDC] score 0)

Although data for a separate consideration of the patient population with favourable risk profile from the adjusted indirect comparison of nivolumab + cabozantinib versus pembrolizumab + axitinib as ACT for research question 1 would have been available, the company did not present corresponding analyses. Thus, no suitable data were available to derive the added benefit of nivolumab + cabozantinib for research question 1.

Research question 2: patients with intermediate (IMDC score 1-2) or poor (IMDC score ≥ 3) risk profile

For research question 2, the company did not choose from the 3 possible treatment options of the ACT, so that the conclusion on the added benefit must primarily be made against the entirety of the treatment options for the ACT, e.g. based on meta-analyses under joint consideration of all studies. Although data for a separate consideration of the patient population with intermediate or poor risk profile would have been available from the adjusted indirect comparison of nivolumab + cabozantinib versus the 3 treatment options of the ACT, the company did not conduct such meta-analytical consideration. Therefore, no suitable data were available for research question 2 either.

Results for research questions 1 and 2

The company presented no suitable data for the assessment of the added benefit of nivolumab + cabozantinib in comparison with the ACT in adult patients with treatment-naive advanced renal cell carcinoma, neither for research question 1 (patients with poor risk profile) nor for research question 2 (patients with intermediate or poor risk profile).

In each case, this resulted in no hint of an added benefit of nivolumab + cabozantinib in comparison with the ACT for these patients; an added benefit is therefore not proven.

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

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

[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].

Table 3: Nivolumab + cabozantinib – 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 renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven
2	Adult patients with treatment-naive advanced renal cell carcinoma 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	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
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 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 nivolumab in combination with cabozantinib (hereinafter referred to as "nivolumab + cabozantinib") in comparison with the ACT in adult patients with treatment-naive advanced renal cell carcinoma.

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 nivolumab + cabozantinib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with treatment-naive advanced renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib
2	Adult patients with treatment-naive advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor (IMDC score ≥ 3) risk profile[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.
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 named the options specified by the G-BA, but additionally listed sunitinib and pazopanib as recommended treatment options, whereby it considered sunitinib to be particularly relevant. This deviation is not appropriate. The company did not cite any sources that adequately justify the additional consideration of sunitinib and pazopanib in the framework of the ACT. 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 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on nivolumab + cabozantinib (status: 17 March 2021)
- bibliographical literature search on nivolumab + cabozantinib (last search on 10 March 2021)
- search in trial registries/trial results databases for studies on nivolumab + cabozantinib (last search on 16 March 2021)
- search on the G-BA website for nivolumab + cabozantinib (last search on 24 March 2021)
- bibliographical literature search on the ACT (last search on 15 March 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 17 March 2021)
- search on the G-BA website for the ACT (last search on 24 March 2021)

The completeness of the study pool was checked by:

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

Direct comparison

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

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 1 relevant RCT on the comparison with sunitinib:

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

In the next step, the company searched for RCTs with the ACT. In doing so, it stated having considered only RCTs versus sunitinib when selecting relevant studies.

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 nivolumab + cabozantinib and thus no further relevant common comparator for a possible adjusted indirect comparison.

On the side of the ACT, the company identified a total of 3 RCTs:

- KEYNOTE-426 (MK-3475-426): pembrolizumab + axitinib vs. sunitinib [8]
- CA209-214 (CheckMate 214): nivolumab + ipilimumab vs. sunitinib [9]
- JAVELIN Renal 101: avelumab + axitinib vs. sunitinib [10]

For the company, a total of 3 indirect comparisons resulted from its study pool. The indirect comparisons presented by the company were unsuitable to enable separate conclusion on the added benefit of nivolumab + cabozantinib for patients of research questions 1 and 2 (see below). Therefore, the completeness of the study pool on the side of the ACT was not checked.

The unadjusted indirect comparison presented by the company are unsuitable for the present benefit assessment

In Module 4 M, the company presented the following 3 indirect comparisons (see Figure 1 to Figure 3).

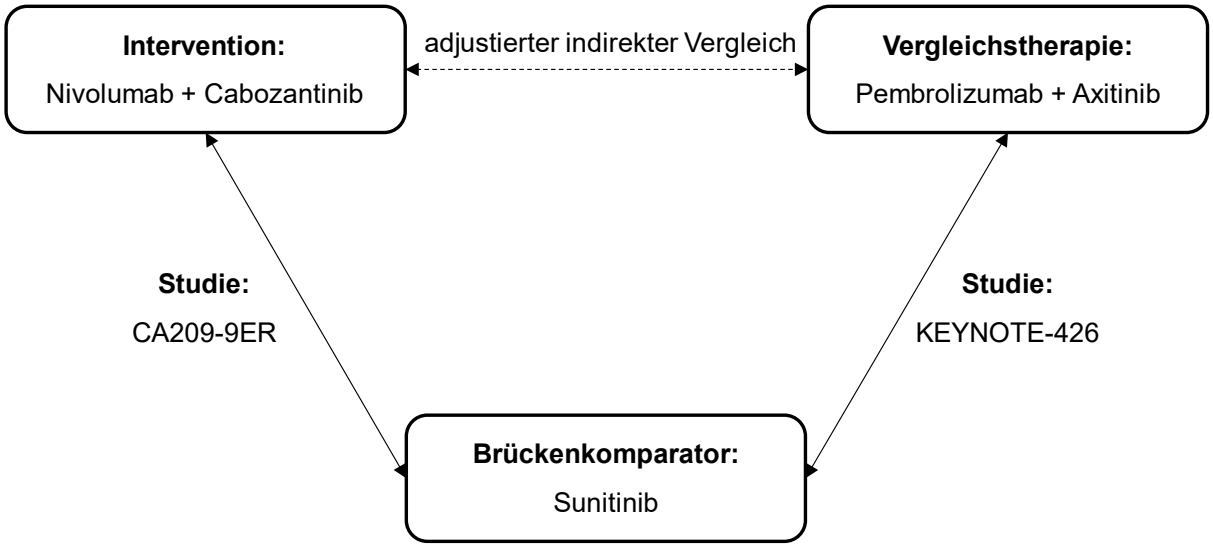

Figure 1: Study pool of the company for the indirect comparison of nivolumab + cabozantinib versus pembrolizumab + axitinib

Adjustierter indirekter Vergleich:	adjusted indirect comparison
Vergleichstherapie:	comparator therapy
Studie:	study
Brückenkomparator:	common comparator

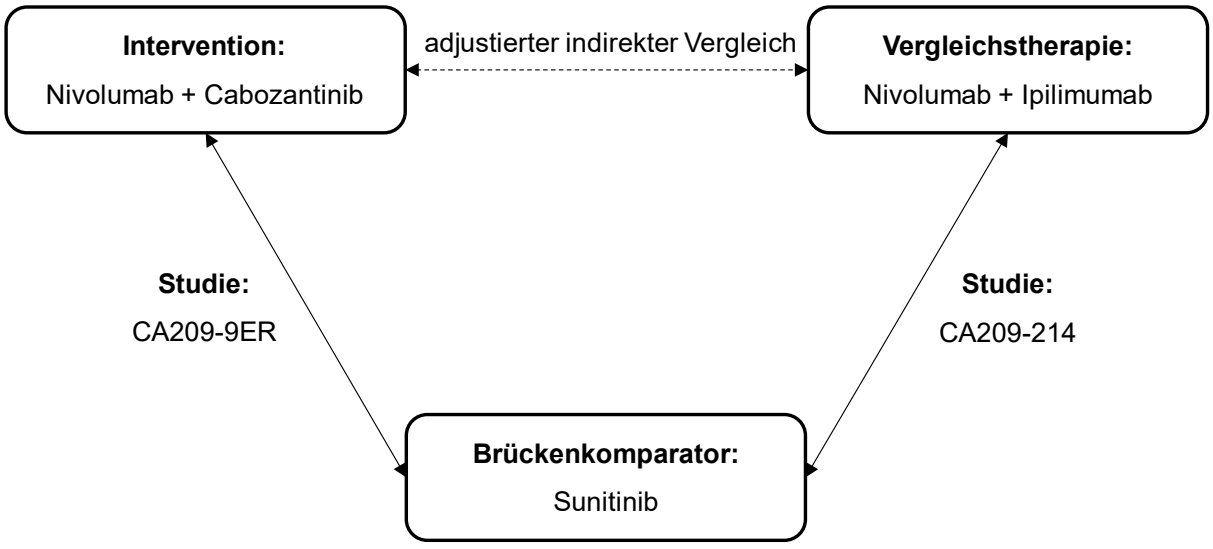

Figure 2: Study pool of the company for the indirect comparison of nivolumab + cabozantinib versus nivolumab + ipilimumab

Adjustierter indirekter Vergleich:	adjusted indirect comparison
Vergleichstherapie:	comparator therapy
Studie:	study
Brückenkomparator:	common comparator

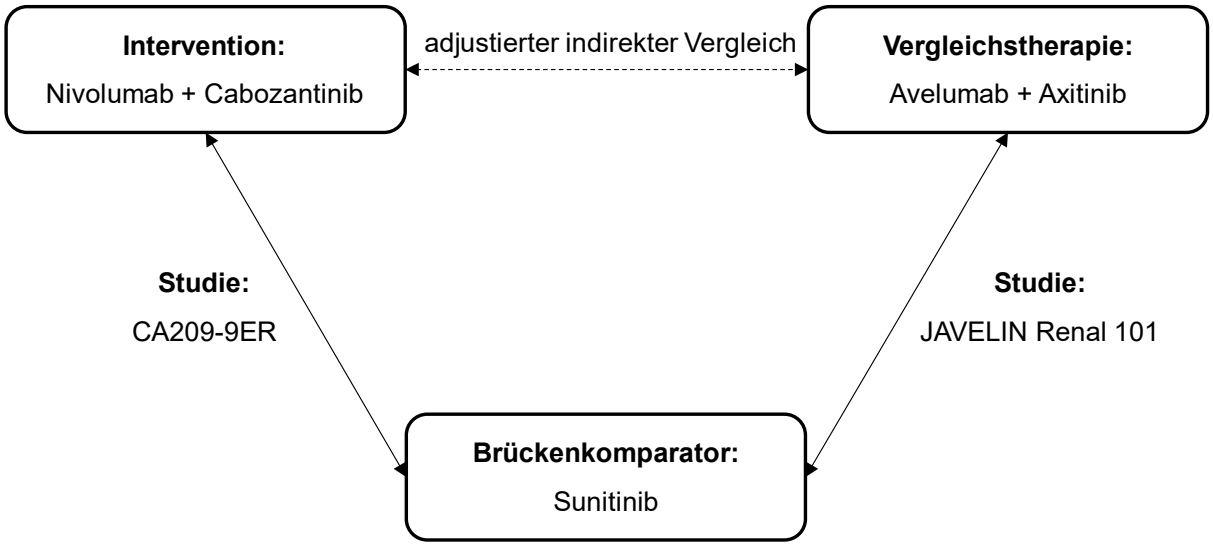

Figure 3: Study pool of the company for the indirect comparison of nivolumab + cabozantinib versus avelumab + axitinib

Adjustierter indirekter Vergleich:	adjusted indirect comparison
Vergleichstherapie:	comparator therapy
Studie:	study
Brückenkomparator:	common comparator

On the basis of these 3 indirect comparisons, the company considered the following different patient populations depending on the treatment option:

a) Nivolumab + cabozantinib versus pembrolizumab + axitinib: patients with any risk profile

   The company explained its approach in this indirect comparison by stating that the G-BA specified pembrolizumab + axitinib as ACT in both research questions (favourable risk profile as well as intermediate or poor risk profile).

b) Nivolumab + cabozantinib versus nivolumab + ipilimumab: patients with intermediate or poor risk profile

c) Nivolumab + cabozantinib versus avelumab + axitinib: patients with poor risk profile

The company presented the results obtained from these 3 indirect comparisons for the respective patient population under consideration. The company did not allocate the results to the separate research questions 1 (favourable risk profile) and 2 (intermediate or poor risk profile).

The company's approach is not suitable to make separate conclusions on the added benefit of nivolumab + cabozantinib for patients with favourable risk profile (research question 1) and patients with intermediate or poor risk profile (research question 2). Below, this is explained separately for research questions 1 and 2.

2.4 Research question 1: patients with favourable risk profile (IMDC score 0)

As described in Section 2.3, the company presented a total of 3 adjusted indirect comparisons of nivolumab + cabozantinib versus different therapies in Module 4 M (see figures 1 to 3), without assigning the results to the separate research questions 1 (favourable risk profile) and 2 (intermediate or poor risk profile). The company presented no separate analyses for the patient populations of research question 1.

The approach of the company was not appropriate. The adjusted indirect comparison of nivolumab + cabozantinib (study CA209-9ER) versus pembrolizumab + axitinib (study KEYNOTE-426) mentioned as ACT for research question 1 in Section 2.3 under a) considers the population of patients across all risk profiles. Thus, it also includes data for the patient population of research question 1.

In Module 4 M on the KEYNOTE-426 study, the company names 2 sources providing separate results for the patient group with a favourable risk profile [11,12]. The company would thus have been able to conduct an indirect comparison of nivolumab + cabozantinib versus pembrolizumab + axitinib for the patients of research question 1. There is no justification as to why the company did not conduct such analyses.

Overall, Module 4 M provides no suitable data for the assessment of nivolumab + cabozantinib for the patient population with a favourable risk profile.

At this point, reference should be made to benefit assessment A21-49 Cabozantinib (renal cell carcinoma) on the identical therapeutic indication of the present benefit assessment [13]. Benefit assessment A21-49 shows that overall, neither advantages nor disadvantages for the combination of cabozantinib + nivolumab versus the ACT pembrolizumab + axitinib are shown for research question 1 (favourable risk profile). [13].

2.4.1 Results on added benefit

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

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

2.4.2 Probability and extent of added benefit

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

This assessment deviates from that of the company, which, based on the results of RCT CA209-9ER, derived an indication of a major added benefit of nivolumab + cabozantinib in a direct comparison with sunitinib and, based on the 3 submitted adjusted indirect comparisons versus avelumab + axitinib, nivolumab + ipilimumab and pembrolizumab + axitinib, derived a hint of a non-quantifiable added benefit for all patients in the present therapeutic indication, irrespective of the risk profile.

2.5 Research question 2: patients with intermediate (IMDC score 1-2) or poor (IMDC score ≥ 3) risk profile

As described in Section 2.3, the company presented a total of 3 adjusted indirect comparisons of nivolumab + cabozantinib versus the 3 different ACT options in Module 4 M (see figures 1 to 3), without assigning the results to the separate research questions 1 (favourable risk profile) and 2 (intermediate or poor risk profile). The company presented no separate analyses for the patient populations of research question 2 taking into account all 3 treatment options.

The approach of the company was not appropriate. As the company did not choose from the 3 possible ACT treatment options, the conclusion on the added benefit must primarily be made against the entirety of the treatment options for the ACT, e.g. based on meta-analyses under joint consideration of all studies [14]. Each of the 3 adjusted indirect comparisons conducted by the company yield data for the patient population with intermediate or poor risk profile. For conclusions on the patient population of research question 2, it is therefore necessary to consider the summarized entire evidence available for this patient population.

This is also possible for the company in the present situation, as separate analyses on the adjusted indirect comparison of nivolumab + cabozantinib versus pembrolizumab + axitinib are available for the patient group with an intermediate or poor risk profile mentioned in Section 2.3 under a). In Module 4 M, the company cited corresponding sources from which this information can be taken [11,12]. A meta-analytical consideration of these separate results together with the results of the two other indirect comparisons conducted by the company for the patient population with intermediate or poor risk profile is therefore possible and also necessary.

Overall, the company presented no suitable data that would allow a conclusion on the added benefit compared to the ACT for patients with intermediate or poor risk profile. The adjusted indirect comparisons presented by the company are not suitable for answering the present research question.

Irrespective of this, no relevant advantages or disadvantages of nivolumab + cabozantinib are shown even when considering the 3 adjusted indirect comparisons submitted by the company. A statistically significant difference versus nivolumab + ipilimumab is shown for the outcome "serious adverse events (SAEs)"; for the outcome "symptoms (Functional Assessment of Cancer Therapy - Kidney Symptom Index - Disease-related Symptoms [FKSI-DRS])" there is a statistically significant difference compared to pembrolizumab + axitinib. However, for the results on SAEs, there is a high risk of bias at least on the side of nivolumab + cabozantinib due to potentially informative censoring (see benefit assessment A21-49 Cabozantinib [renal cell carcinoma] [1]), so that the requirements for the certainty of results for carrying out an adjusted indirect comparison for this outcome are not met. The results for the outcome "symptomatology" (recorded with the FKSI-DRS) are also not usable. This is due to unequal documentation times in the study arms of the KEYNOTE 426 study (see benefit assessment A21-49 Cabozantinib [renal cell carcinoma] [13]).

Moreover, as in research question 1, reference should be made to benefit assessment A21-49 Cabozantinib (renal cell carcinoma) on the identical therapeutic indication of the present benefit assessment [13]. Benefit assessment A21-49 contains relevant results on the added benefit of cabozantinib + nivolumab for the patient population of research question 2 (intermediate or poor risk profile) from an adjusted indirect comparison versus pembrolizumab + axitinib. The assessment results in the conclusion that, overall, there are neither advantages nor disadvantages for the combination of cabozantinib + nivolumab compared to the ACT for the patients of research question 2 [13].

2.5.1 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of nivolumab + cabozantinib in comparison with the ACT in adult patients with treatment-naive advanced renal cell carcinoma with intermediate (IMDC score 1-2) or poor (IMDC score ≥ 3) risk profile. This resulted in no hint of an added benefit of nivolumab + cabozantinib in comparison with the ACT for these patients; an added benefit is therefore not proven.

2.5.2 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of nivolumab + cabozantinib versus the ACT in adult patients with treatment-naive advanced renal cell carcinoma with intermediate (IMDC-Score 1-2) or poor (IMDC score ≥ 3) risk profile, the added benefit of nivolumab + cabozantinib is not proven for these patients.

This assessment deviates from that of the company, which, based on the results of RCT CA209-9ER, derived an indication of a major added benefit of nivolumab + cabozantinib in a direct comparison with sunitinib and, based on the 3 submitted adjusted indirect comparisons versus avelumab + axitinib, nivolumab + ipilimumab and pembrolizumab + axitinib, derived a hint of a non-quantifiable added benefit for all patients in the present therapeutic indication, irrespective of the risk profile.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of nivolumab + cabozantinib in comparison with the ACT is summarized in Table 5.

Table 5: Nivolumab + cabozantinib – 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 renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven
2	Adult patients with treatment-naive advanced renal cell carcinoma 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	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
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 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.

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