IQWiG Reports – Commission No. A21-163

Pembrolizumab (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 *Pembrolizumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 5 April 2022). Please note: This document was translated by an external translator and 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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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

- C. F. Dietrich

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.

Patient and family involvement

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Bent Müller
- Tatjana Hermanns
- Wiebke Hoffman-Eßer
- Deborah Ingenhag-Reister
- Michaela Florina Kerekes
- Matthias Maiworm
- Anja Schwalm
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
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
MSKCC	Memorial Sloan Kettering Cancer Center
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pembrolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 December 2021.

Research question

The aim of the present report is to assess the added benefit of pembrolizumab in combination with lenvatinib (hereinafter referred to as "pembrolizumab + lenvatinib") in comparison with the appropriate comparator therapy (ACT) in adults with previously untreated, advanced renal cell carcinoma.

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

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

Research question	Therapeutic indication	ACT[a]
1	Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib
2	Adults with previously untreated, 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 a poor risk profile) or ▪ Nivolumab in combination with ipilimumab or ▪ **Pembrolizumab in combination with axitinib**

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to 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 2 risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Against this background, the dossier was to present subgroup analyses for patients with intermediate versus poor risk profiles.

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 listed the options specified by the G-BA and selected pembrolizumab in combination with axitinib (hereafter referred to as "pembrolizumab + axitinib") as the ACT for both research questions, but it additionally listed sunitinib as a relevant treatment option with any risk profile. This deviation is not appropriate. The company did not cite any sources to adequately justify the inclusion of sunitinib as an ACT option. Each of the ACT options cited by the G-BA has shown 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 is not an option. The present benefit

assessment of pembrolizumab + lenvatinib was conducted in comparison with the ACT specified by the G-BA.

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

Study pool and study design

No relevant randomized controlled trial (RCT) was found for the direct comparison of pembrolizumab + lenvatinib in comparison with the ACT specified by the G-BA. The company has presented an adjusted indirect comparison using the common comparator of sunitinib, using the CLEAR study for the lenvatinib + pembrolizumab side and the KEYNOTE 426 study for the pembrolizumab + axitinib side of the comparison.

CLEAR study

The CLEAR study is a randomized, open-label, active-control study comparing pembrolizumab + lenvatinib as well as lenvatinib + everolimus with sunitinib. The study enrolled adults with advanced renal cell carcinoma with a clear-cell component. Patients were not allowed to have received any prior systemic therapy. Study exclusion criteria were renal cell carcinoma without clear-cell component, a Karnofsky Performance Status (KPS) < 70%, and active brain metastases.

A total of 1069 patients were randomly assigned at a 1:1:1 ratio to treatment with lenvatinib + everolimus (N = 357), pembrolizumab + lenvatinib (N = 355), or sunitinib (N = 357). The lenvatinib + everolimus treatment arm is neither relevant for the present benefit assessment nor discussed hereinafter.

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

Relevant subpopulation of the CLEAR study

For research question 1, the relevant subpopulation comprises CLEAR participants in either the pembrolizumab + lenvatinib arm or the sunitinib arm who have a favourable risk profile, defined as an International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score of 0. A total of 110 patients in the pembrolizumab + lenvatinib arm and 124 patients in the sunitinib arm exhibited a favourable baseline risk profile as measured with the IMDC score.

For research question 2, the relevant subpopulation consists of CLEAR study participants in either the pembrolizumab + lenvatinib arm or the sunitinib arm who have an intermediate (IMDC score 1 to 2) or poor (IMDC score ≥ 3) risk profile. A total of 243 patients in the pembrolizumab + lenvatinib arm and 229 patients in the sunitinib arm exhibited an intermediate or poor baseline risk profile as per IMDC score.

Study KEYNOTE 426

The KEYNOTE 426 study is a randomized, open-label, active-control approval study comparing pembrolizumab + axitinib versus sunitinib. The study included adults with advanced or metastatic clear-cell renal cell carcinoma (stage IV according to the American Joint Committee on Cancer [AJCC] classification system). Patients were not allowed to have received any prior systemic therapy in the advanced stage, and any adjuvant or neoadjuvant therapy had to have been received more than 12 months prior to study start. Patients had to be in good general health (KPS ≥ 70%). Patients with non-clear cell renal cell carcinoma, those with a KPS < 70%, and those with active brain metastases were excluded from the study.

A total of 861 patients were randomly allocated at a 1:1 ratio to treatment with pembrolizumab + axitinib (N = 432) or 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.

Relevant subpopulations of the KEYNOTE 426 study

The relevant subpopulation for research question 1 comprises KEYNOTE 426 participants with a favourable risk profile (IDMC score 0). These criteria were met by 138 patients in the pembrolizumab + axitinib arm and 131 patients in the sunitinib arm.

The relevant subpopulation for research question 2 comprises KEYNOTE 426 participants with an intermediate (IMDC 1 to 2) or poor risk profile (IMDC ≥ 3). These criteria were met by 294 patients in the pembrolizumab + axitinib arm and 298 patients in the sunitinib arm.

Data cut-offs

The CLEAR and KEYNOTE 426 studies are still ongoing. To date, 4 data cut-offs have been conducted in each of them. The analyses submitted by the company, however, were mainly based on the 3rd data cut-off for the CLEAR study and exclusively on the 3rd data cut-off for the KEYNOTE 426 study. Neither for the CLEAR study nor for the KEYNOTE 426 study does the company's Module 4 A use any results from the current 4th data cut-off for calculating the indirect comparison.

This approach is not appropriate. According to the dossier template, complete analyses must be carried out and presented for all surveyed patient-relevant outcomes at all data cut-offs relevant for the benefit assessment. The presentation of results from a particular data cut-off can be foregone only if the data cut-off is expected to offer no substantial additional information compared to another data cut-off.

Limited available information precludes assessment of similarity of the relevant subpopulations from the CLEAR and KEYNOTE 426 studies

The similarity check was to be carried out using the relevant subpopulations. However, neither for the subpopulation relevant for research question 1 (favourable risk profile) nor for the

subpopulation relevant for research question 2 (intermediate or poor risk profile) are data available on patient characteristics, treatment and follow-up durations, or prior and subsequent therapies received. Therefore, the subpopulations cannot be inferred with acceptable certainty to be sufficiently similar for an indirect comparison.

Irrespective of this problem, it was impossible to draw any conclusions on added benefit regarding research question 1 or research question 2 from the indirect comparison of the CLEAR and KEYNOTE 426 studies for the outcomes of the morbidity, health-related quality of life, or side effects categories. Hence, even if the relevant subpopulations of the CLEAR and KEYNOTE 426 studies were assumed to be sufficiently similar, only the outcome of overall survival would be suitable for analysis. The results for the outcome of overall survival presented by the company's Module 4 A show no statistically significant difference between pembrolizumab + lenvatinib versus pembrolizumab + axitinib for the subpopulation relevant for research question 1 (favourable risk profile) nor for the subpopulation relevant for research question 2 (intermediate and poor risk profiles).

Results

No suitable data for the assessment of added benefit in comparison with the ACT are available for assessing pembrolizumab + lenvatinib in adults with previously untreated advanced renal cell carcinoma with a favourable risk profile (research question 1) or in adults with an intermediate or poor risk profile (research question 2).

This results in no hint of added benefit of pembrolizumab + lenvatinib in comparison with the ACT for any of these patients; added benefit is therefore not proven.

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

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

[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: Pembrolizumab + lenvatinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven
2	Adults with previously untreated, 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 a poor risk profile) or ▪ Nivolumab in combination with ipilimumab or ▪ **Pembrolizumab in combination with axitinib**	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to 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 2 risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Against 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 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 to assess the added benefit of pembrolizumab in combination with lenvatinib (hereinafter referred to as "pembrolizumab + lenvatinib") in comparison with the ACT in adults with previously untreated, advanced renal cell carcinoma.

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

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

Research question	Therapeutic indication	ACT[a]
1	Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib
2	Adults with previously untreated, 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 a poor risk profile), or ▪ Nivolumab in combination with ipilimumab, or ▪ **Pembrolizumab in combination with axitinib**

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to 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 2 risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Against this background, the dossier was to present subgroup analyses for patients with intermediate versus poor risk profiles.

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 listed the options specified by the G-BA and selected pembrolizumab in combination with axitinib (hereafter referred to as "pembrolizumab + axitinib") as the ACT for both research questions, but it additionally listed sunitinib as a relevant treatment option with any risk profile. This deviation is not appropriate. The company did not cite any sources to adequately justify the additional taking into account of sunitinib as an ACT. Each of the ACT options cited by the G-BA showed considerable added benefit versus sunitinib [3-5]. The German S3 guideline likewise reflects this situation, recommending sunitinib only for patients who are not candidates for checkpoint inhibitor-based combination therapy [6]. The present benefit assessment of pembrolizumab + lenvatinib was conducted in comparison with the ACT specified by the G-BA.

The assessment is 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 pembrolizumab + lenvatinib (status: 15 November 2021)
- bibliographical literature search on pembrolizumab + lenvatinib (last search on 19 October 2021)
- search in trial registries / trial results databases for studies on pembrolizumab + lenvatinib (last search on 19 October 2021)
- search on the G-BA website for pembrolizumab + lenvatinib (last search on 20 October 2021)
- bibliographical literature search on the ACT (last search on 19 October 2021)
- search in trial registries / trial results databases for studies on the ACT (last search on 19 October 2021)
- search on the G-BA website for the ACT (last search on 20 October 2021)

To check the completeness of the study pool:

- search in trial registries for studies on pembrolizumab (last search on 20 January 2022); for search strategies, see Appendix A of the full dossier assessment

The search on pembrolizumab comprised the check of completeness of the study pool both on the pembrolizumab + lenvatinib side and on the side of the ACT chosen by the company, pembrolizumab + axitinib. The check did not identify any additional relevant study.

Direct comparison

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

However, the company derived added benefit using the CLEAR study as a direct comparator study for pembrolizumab + lenvatinib in comparison with sunitinib, which it deemed a relevant treatment option (see Section 2.2). In the present benefit assessment versus the ACT, the CLEAR study is relevant only for the indirect comparison, and below, it is therefore discussed only in the context of the indirect comparison.

Indirect comparison

Because the company identified no RCTs comparing against 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 to be assessed, pembrolizumab + lenvatinib, and identified 1 relevant RCT on the comparison with sunitinib:

- CLEAR: pembrolizumab + lenvatinib versus sunitinib

For the indirect comparison, the company conducted an information retrieval for studies with pembrolizumab + axitinib and the common comparator of sunitinib. Restricting the common

comparator to sunitinib is appropriate because the check of the completeness of the study pool identified no other relevant RCT with pembrolizumab + lenvatinib and thus no other relevant common comparator for a potential adjusted indirect comparison.

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

- KEYNOTE 426: pembrolizumab + axitinib versus sunitinib

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

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, indirect comparison: pembrolizumab + lenvatinib versus pembrolizumab + axitinib

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])
Pembrolizumab + lenvatinib vs. sunitinib						
E7080-G000-307 or KEYNOTE 581 (CLEAR[d])	Yes	No[e]	No	Yes [7,8]	Yes [9-11]	Yes [12,13]
Pembrolizumab + axitinib vs. sunitinib						
MK-3475-426 (KEYNOTE 426[d])	No	Yes	No	Yes [14-16]	Yes [17-20]	Yes [21-25]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial 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 by this acronym.
e. The company is collaborator.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that selected by the company for the indirect comparison.

The KEYNOTE 426 study has already been submitted and assessed in a prior benefit assessment of pembrolizumab + axitinib (dossier assessment A19-99) as well as in the context of an indirect comparison used in the benefit assessment of cabozantinib + nivolumab (dossier assessment A21-49) [26,27].

Figure 1 schematically presents the indirect comparison.

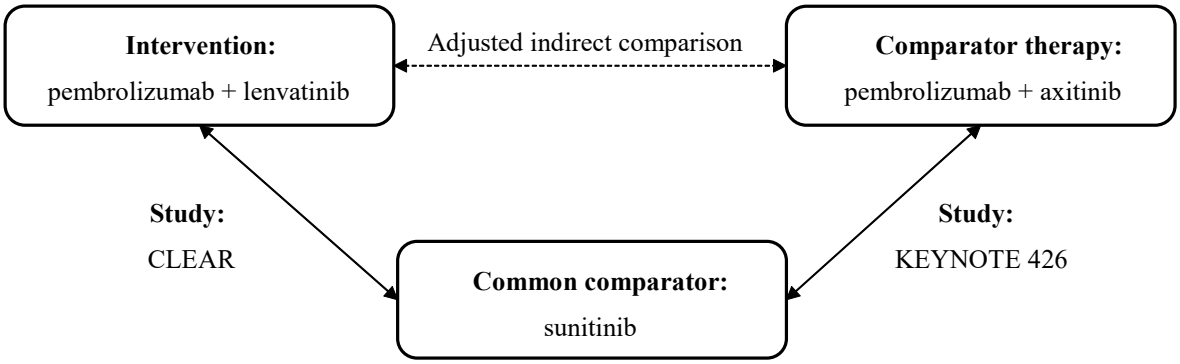

Figure 1: Study pool for the indirect comparison of pembrolizumab + lenvatinib versus pembrolizumab + axitinib

2.3.2 Study characteristics

2.3.2.1 Study design

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

Table 6: Characterization of the included studies – RCT, indirect comparison: pembrolizumab + lenvatinib versus pembrolizumab + axitinib (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Pembrolizumab + lenvatinib vs. sunitinib						
CLEAR	RCT, open-label, parallel-group	Adults with previously untreated, advanced renal cell carcinoma[b] and Karnofsky Performance Status ≥ 70%	Pembrolizumab + lenvatinib (N = 355) Everolimus + lenvatinib (N = 357)[c] Sunitinib (N = 357) Relevant subpopulations thereof: <u>Research question 1[d]:</u> Pembrolizumab + lenvatinib (n = 110) Sunitinib (n = 124) <u>Research question 2[e]:</u> Pembrolizumab + lenvatinib (n = 243) Sunitinib (n = 229)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, or upon the physician's or patient's discretion ; pembrolizumab was to be administered for a maximum of 35 cycles (2 years)[f] Follow-up observation[g]: outcome-specific, at the longest until death, consent withdrawal, or study end	181 centres in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Ireland, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, Switzerland, United Kingdom, United States 10/2016–ongoing <u>Data cut-offs:</u> 6/12/2018[h] 15/11/2019[i] 28/08/2020[j] 31/03/2021[k]	Primary: PFS Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, indirect comparison: pembrolizumab + lenvatinib versus pembrolizumab + axitinib (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-group	Adults with previously untreated, advanced or metastatic renal cell carcinoma[l] (AJCC stage IV) and Karnofsky Performance Status ≥ 70%	Pembrolizumab + axitinib (N = 432) Sunitinib (N = 429) Relevant subpopulations thereof: <u>Research question 1[d]:</u> Pembrolizumab + axitinib (n = 138) Sunitinib (n = 131) <u>Research question 2[e]:</u> Pembrolizumab + axitinib (n = 294) Sunitinib (n = 298)	Screening: ≤ 28 days Treatment: until disease progression, unacceptable toxicity, or upon the physician's or patient's discretion; pembrolizumab was to be administered for a maximum of 35 cycles (2 years)[m] Follow-up observation[g]: outcome-specific, at the longest until death, consent withdrawal, or study end	A total of 129 centres in Brazil, Canada, Czech Republic, France, Germany, Hungary, Ireland, Japan, Poland, Russia, Spain, South Korea, Taiwan, Ukraine, United Kingdom, United States 10/2016–ongoing <u>Data cut-offs:</u> 24/08/2018[n] 2/01/2019[o] 6/01/2020[p] 11/01/2021[q]	Primary: overall survival, PFS Secondary: symptoms, health status, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, indirect comparison: pembrolizumab + lenvatinib versus pembrolizumab + axitinib (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 include only information on relevant available outcomes for this benefit assessment.
b. Histologically or cytologically confirmed renal cell carcinoma with clear-cell component.
c. This arm is neither relevant for the benefit assessment nor presented in the following tables.
d. Patients with a favourable risk profile (IMDC score of 0).
e. Patients with an intermediate risk profile (IMDC score 1–2) or poor risk profile (IMDC score ≥ 3).
f. In case of complete response, treatment termination was allowed under certain conditions. Treatment beyond disease progression (as determined using RECIST 1.1) was allowed, provided the treating physician deemed it to be well tolerated and to promise clinical benefit for the patient.
g. Outcome-specific information is provided in Table 8.
h. Predefined ORR and DOR interim analysis of the first 88 patients in the lenvatinib + pembrolizumab arm, with a median follow-up of 12 months and a minimum DOR follow-up of 6 months.
i. Predefined interim analysis conducted about 4 months after randomization of the last patient and about 310 PFS events in the lenvatinib + pembrolizumab and sunitinib arms.
j. Predefined interim analysis of overall survival and final analysis of the primary outcome of PFS, to occur after 388 PFS events for each comparison.
k. Analysis of overall survival for approval procedure.
l. Histologically confirmed renal cell carcinoma with a clear-cell component and sarcomatoid features.
m. In case of confirmed complete response, it was possible to terminate treatment under certain conditions. After the end of pembrolizumab treatment (after complete response or after 35 cycles), patients with subsequent confirmed progression were allowed to start another round of pembrolizumab treatment for another year ("second course phase").
n. Predefined interim analysis, planned to take place after at least 305 PFS events had occurred and all patients had completed at least 7 months of post-randomization follow-up.
o. Upon EMA request.
p. Discrepant information provided in Module 4 A and the study documents; according to Module 4 A, this data cut-off was requested by the FDA; based on the study documents, however, this appears to be the predefined interim analysis scheduled for the time at which 74% of the ultimately required events for the outcome of overall survival (or 299 deaths) had occurred.
q. Predefined final analysis after 404 deaths.

AE: adverse event; AJCC: American Joint Committee on Cancer; DOR: duration of response; EMA: European Medicines Agency; FDA: Food and Drug Administration; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; n: relevant subpopulation; N: number of randomized patients; ORR: objective response rate; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumors

Table 7: Characteristics of the intervention – RCT, indirect comparison: pembrolizumab + lenvatinib versus pembrolizumab + axitinib (multipage table)

Study	Intervention / comparator therapy	Common comparator
Pembrolizumab + lenvatinib vs. sunitinib		
CLEAR	Pembrolizumab 200 mg every 3 weeks, i. v. + Lenvatinib 20 mg/day, orally **Dose adjustments** Pembrolizumab: ▪ no dose adjustment allowed ▪ Treatment discontinuations due to toxicity allowed for ≤ 12 weeks[a] Lenvatinib: ▪ Treatment discontinuation or 3-step dose reduction down to minimum dose of 8 mg/day due to toxicity allowed; no reescalation allowed	Sunitinib 50 mg/day, orally Duration of cycle: 6 weeks (4 weeks of treatment, followed by a 2-week rest period) ▪ Treatment discontinuation or 2 dose reductions due to toxicity in 12.5 mg steps down to the minimum dose of 25 mg allowed; no reescalation allowed. ▪ Dose reductions or escalations allowed if a CYP3A4 inhibitor or inducer is necessary
	Non-permitted pretreatment ▪ Radiotherapy ≤ 21 days before randomization[b] ▪ Systemic therapy of renal cell carcinoma including VEGF-targeted therapy ▪ Investigational drugs ≤ 4 weeks before the start of study treatment ▪ Immunosuppressant medications ≤ 7 days before the start of study treatment **Permitted concomitant treatment** ▪ Bisphosphonates or denosumab ▪ Palliative radiotherapy in patients with up to 2 painful, preexisting bone metastases ▪ Premedication due to infusion-related reactions (to pembrolizumab) in the intervention arm (antihistamines, antipyretics) **Non-permitted concomitant treatment** ▪ Other cancer therapies (e.g. chemotherapy, TKI, radiotherapy [except palliative], surgical resection and debulking, immunotherapy) ▪ Only pembrolizumab + lenvatinib arm: systemic glucocorticoids (except for prophylactic therapy of allergic reactions and for the treatment of immune-related AEs) ▪ Other investigational preparations	

Table 7: Characteristics of the intervention – RCT, indirect comparison: pembrolizumab + lenvatinib versus pembrolizumab + axitinib (multipage table)

Study	Intervention / comparator therapy	Common comparator
Pembrolizumab + axitinib vs. sunitinib		
KEYNOTE-426	Pembrolizumab 200 mg every 3 weeks, i. v. + Axitinib 5 mg orally, twice daily **Dose adjustments** Pembrolizumab: ▪ no dose adjustment allowed ▪ Treatment discontinuations due to toxicity allowed for ≤ 12 weeks[a] Axitinib: ▪ in the absence of AEs (> CTCAE grade 2), dose increases allowed to 7 mg after 6 weeks and to 10 mg after another 6 weeks ▪ 2 dose reductions allowed[c] ▫ 3 mg twice daily ▫ 2 mg twice daily ▪ Treatment discontinuations due to toxicity allowed for ≤ 3 weeks	Sunitinib 50 mg/day, orally Duration of cycle: 6 weeks (4 weeks of treatment, followed by a 2-week rest period) ▪ Treatment discontinuation or 2 dose reductions due to toxicity allowed in 12.5 mg increments down to the minimum dose of 25 mg[c], followed by reescalation, also in 12.5 mg increments ▪ Dose reductions or escalations allowed if a CYP3A4 inhibitor or inducer is necessary
	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 against advanced renal cell carcinoma or within the last 2 years in active autoimmune disorders ▪ Major surgeries ≤ 4 weeks before randomization ▪ Other investigational drugs ≤ 4 weeks before randomization ▪ Radiotherapy ≤ 2 weeks before randomization ▪ Immunosuppressant medications ≤ 7 days prior to randomization[d] ▪ Potent CYP3A4/5 inhibitors or inducers ≤ 7 days before randomization **Permitted concomitant treatment** ▪ Bisphosphonates or RANKL inhibitors (if started > 2 weeks prior to randomization) ▪ Premedication due to infusion-related reactions (caused by pembrolizumab) in the intervention arm (antihistamines, analgesics) ▪ Symptomatic radiotherapy of individual lesions or of the brain after consultation with the sponsor **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: pembrolizumab + lenvatinib versus pembrolizumab + axitinib (multipage table)

Study	Intervention / comparator therapy	Common comparator
a. Any need for an extended interruption led to the drug's permanent discontinuation. b. Palliative radiotherapy of bone metastases was allowed if completed 2 weeks prior to the start of the study medication. c. Any further dose reduction led to permanent discontinuation of the drug. d. Exception: CNS metastases. AE: adverse event; CNS: central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; CYP3A4: cytochrome P450 3A4; i.v.: intravenous; mTOR: mechanistic Target of Rapamycin; PD-1: programmed cell death protein 1; PD-PD-L1 / L2: programmed death ligand 1/2; RANKL: receptor activator of NF-κB ligand; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor		

CLEAR study

The CLEAR study is a randomized, open-label, active-control study comparing pembrolizumab + lenvatinib as well as lenvatinib + everolimus with sunitinib. The study enrolled adults with advanced renal cell carcinoma with a clear-cell component. Patients were not allowed to have received any prior systemic therapy. Study exclusion criteria were renal cell carcinoma without clear-cell component, a KPS < 70%, and active brain metastases.

A total of 1069 patients were randomly assigned at a 1:1:1 ratio to treatment with lenvatinib + everolimus (N = 357), pembrolizumab + lenvatinib (N = 355), or sunitinib (N = 357). Randomization was stratified by region (Western Europe and North America versus rest of the world) and risk group in accordance with Memorial Sloan Kettering Cancer Center (MSKCC) (favourable versus intermediate versus poor). The lenvatinib + everolimus treatment arm is neither relevant for the present benefit assessment nor discussed hereinafter.

Pembrolizumab + lenvatinib treatment as well as sunitinib treatment were administered in accordance with the regimens presented in Table 7 and largely correspond to the specifications of the Summaries of Product Characteristics (SPCs) [28-30].

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

Patients were treated until disease progression, unacceptable toxicity, or treatment discontinuation upon the physician's or patient's discretion. The study limited pembrolizumab treatment to 35 treatment cycles (about 2 years). At the time of the 3rd data cut-off (28 August 2020), 75 patients (21% of the pembrolizumab + lenvatinib arm) had achieved this maximum treatment duration with pembrolizumab. The documents submitted by the company do not contain any data on the last data cut-off (31 March 2021).

The study did not provide for any switching to the treatment of another study arm.

After discontinuation of the study medication, there were no restrictions regarding subsequent therapies. However, the company did not submit any information on subsequent therapies for the relevant subpopulations.

Relevant subpopulation of the CLEAR study

For research question 1, the relevant subpopulation comprises CLEAR participants in either the pembrolizumab + lenvatinib arm or the sunitinib arm who have a favourable risk profile, defined as an IMDC score of 0. The IMDC score was surveyed at baseline alongside the MSKCC score. A total of 110 patients in the pembrolizumab + lenvatinib arm and 124 patients in the sunitinib arm exhibited a favourable baseline risk profile as measured with the IMDC score.

For research question 2, the relevant subpopulation consists of CLEAR study participants in either the pembrolizumab + lenvatinib arm or the sunitinib arm who have an intermediate (IMDC score 1 to 2) or poor (IMDC score ≥ 3) risk profile. A total of 243 patients in the pembrolizumab + lenvatinib arm and 229 patients in the sunitinib arm exhibited an intermediate or poor baseline risk profile according to the IMDC score.

The company's Module 4 A presents analyses on the 2 relevant subpopulations, but in the present situation, these are unsuitable for use in the benefit assessment (as explained in Section 2.3.2.4).

Study KEYNOTE 426

The KEYNOTE 426 study is a randomized, open-label, active-control approval study comparing pembrolizumab + axitinib versus sunitinib. The study included adults with advanced or metastatic clear-cell renal cell carcinoma (stage IV according to the AJCC classification system). Patients were not allowed to have received any prior systemic therapy in the advanced stage, and any adjuvant or neoadjuvant therapy had to have been received more than 12 months prior to study start. Patients had to be in good general health (KPS ≥ 70%). Patients with non-clear cell renal cell carcinoma, those with a KPS < 70%, and those with active brain metastases were excluded from the study.

A total of 861 patients were randomly allocated at a 1:1 ratio to treatment with pembrolizumab + axitinib (N = 432) or 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.

Pembrolizumab + axitinib treatment as well as sunitinib treatment were administered in accordance with the regimens shown in Table 7 and largely correspond to SPC specifications [29-31].

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, unacceptable toxicity, or treatment discontinuation upon the physician's or patient's discretion. Treatment in the intervention arm was limited by the maximum of 35 allowed pembrolizumab treatment cycles (about 2 years). According to information from the Powles 2020 publication [22], 19 patients (4%) had reached the maximum pembrolizumab treatment duration at the 3rd data cut-off (6 January 2020). However, study documents show that this percentage is calculated based on the patients who had completed treatment with both pembrolizumab and lenvatinib. Leaving aside lenvatinib therapy, 129 patients (30% of the pembrolizumab + axitinib arm) had, at this point in time, completed pembrolizumab therapy based on the maximum treatment duration. At the time of the 4th data cut-off (11 January 2021), 136 patients (32% of the pembrolizumab + axitinib arm) had reached this maximum treatment duration for 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. However, the company did not submit any information on subsequent therapies for the relevant subpopulations.

Relevant subpopulations of the KEYNOTE 426 study

The relevant subpopulation for research question 1 comprises KEYNOTE 426 participants with a favourable risk profile (IDMC score 0). These were 138 patients in the pembrolizumab + axitinib arm and 131 patients in the sunitinib arm.

The relevant subpopulation for research question 2 comprises KEYNOTE 426 participants with an intermediate (IMDC 1 to 2) or poor risk profile (IMDC ≥ 3). These criteria were met by 294 patients in the pembrolizumab + axitinib arm and 298 patients in the sunitinib arm.

The company's Module 4 A presents analyses on the 2 relevant subpopulations, but in the present situation, these are unsuitable for use in the benefit assessment (as explained in Section 2.3.2.4).

2.3.2.2 Planned duration of follow-up observation

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

Table 8: Planned duration of follow-up observation – RCT, indirect comparison: pembrolizumab + lenvatinib versus pembrolizumab + axitinib

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
Pembrolizumab + lenvatinib vs. sunitinib	
CLEAR	
Mortality	
Overall survival	At the longest until death, consent withdrawal, or study end
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 120 days after the last dose of the study medication or 30 days after the last dose of the study medication if a new antineoplastic therapy is started
Pembrolizumab + axitinib vs. sunitinib	
KEYNOTE 426	
Mortality	
Overall survival	At the longest until death, consent withdrawal, or study end
Morbidity	
Symptoms (EORTC QLQ-C30[a], FKSI-DRS[a])	Until 30 days after the last dose of the study medication
Health status (EQ-5D VAS[a])	Until 30 days after the last dose of the study medication
Health-related quality of life (EORTC QLQ-C30[a])	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. Starting on 31 January 2020, patient-reported outcomes were no longer surveyed.

AE: adverse event; EORTC: European Organization 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

The follow-up durations for the outcome categories of morbidity, health-related quality of life, and side effects are systematically shortened in both studies because they were surveyed only for the period of treatment with the study medication (plus 30 days or 90 days for serious

adverse events [SAEs] in the KEYNOTE 426 study and 120 days for SAEs in the CLEAR study). For these outcomes, data are therefore available only for the shortened follow-up period. Data on the entire study duration or until death are missing.

2.3.2.3 Data cut-offs

CLEAR study

The CLEAR study is still ongoing. To date, at total of 4 data cut-offs have been carried out:

- 1st data cut-off (6 December 2018): predefined 1st interim analysis of the first 88 patients in the pembrolizumab + lenvatinib arm with a median follow-up period of 12 months and a minimum duration of response of 6 months.
- 2nd data cut-off (15 November 2019): predefined 2nd interim analysis to be conducted about 4 months after randomization of the last patient and about 310 PFS events in the lenvatinib + pembrolizumab and sunitinib arms.
- 3rd data cut-off (28 August 2020): predefined 3rd interim analysis and final analysis for the primary outcome of PFS with 388 PFS events reached per comparison.
- 4th data cut-off (31 March 2021): extraction and analysis of data on overall survival for the approval procedure.

KEYNOTE 426 study

The KEYNOTE 426 study is still ongoing. A total of 4 data cut-offs were conducted:

- 1st data cut-off (24 August 2018): predefined 1st interim analysis to be conducted after 305 events had occurred in the PFS outcome and after all patients had undergone at least 7 months of post-randomization follow-up observation
- 2nd data cut-off (2 January 2019): data cut-off conducted post hoc upon request by the European Medicines Agency (EMA)
- 3rd data cut-off (6 January 2020): predefined 2nd interim analysis to be conducted after 487 events of the PFS outcome and reaching 74% of the ultimately required events for the overall survival outcome (or 299 deaths)
- Final data cut-off (11 January 2021): predefined analysis after reaching 404 events concerning the outcome of overall survival

For the CLEAR study, the company's Module 4 A presents analyses on the 3rd data cut-off. Only for the outcome of overall survival did the company additionally provide analyses on the 4th data cut-off. For the KEYNOTE 426 study, it presented results only from the 3rd data cut-off.

Neither for the CLEAR study nor for the KEYNOTE 426 study, however, did the company's Module 4 A use any results from the current data cut-off to calculate the indirect comparison.

Instead, the company used the results from the 3rd data cut-off of the CLEAR study (28 August 2020) and of the 3rd data cut-off of the KEYNOTE 426 study (6 January 2020). The company justified this choice merely by the 2 data cut-offs having similar follow-up durations.

It is not appropriate to base the selection of data cut-offs for an indirect comparison solely on the similarity of follow-up durations in the 2 studies. According to the dossier template [32], complete analyses must be carried out and presented for all surveyed patient-relevant outcomes at all data cut-offs relevant for the benefit assessment. The presentation of results from a particular data cut-off can be foregone only if the data cut-off is expected to offer no substantial additional information compared to another data cut-off.

2.3.2.4 Limited available information precludes assessment of similarity of the relevant subpopulations from the CLEAR and KEYNOTE 426 studies

A central prerequisite for the inclusion of studies in an adjusted indirect comparison is a similarity check [1,33,34]. 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) as well as methodological factors (e.g. outcome characteristics) must be taken into account [35].

The CLEAR and KEYNOTE 426 studies share a similar study design. Both studies are multicentre, open-label RCTs that included adults with previously untreated, advanced or metastatic renal cell carcinoma. The administration of the common comparator of sunitinib is similar as well. Detailed information on the study design and the interventions in the 2 studies are found in Section 2.3.2.

The company used the comparison of the patient characteristics on the basis of the total population of both studies and rated them as similar. Information on the patient characteristics is not available for the subpopulation relevant for research question 1 (favourable risk profile) nor for the subpopulation relevant for research question 2 (intermediate or poor risk profile). The company reports that the risk profile was a stratification factor in both included studies, and therefore, patient populations are presumably homogeneous not only in the total populations of the individual treatment arms, but also in the subpopulation relevant for the benefit assessment.

The company's approach is not appropriate. As already discussed in benefit assessment A21-49 [26], the similarity check was to be carried out based on the relevant subpopulations. At 33% (CLEAR) and 31% (KEYNOTE 426), the subpopulations relevant for research question 1, patients with a favourable risk profile, make up only a small percentage of the total population of both studies. At 66% (CLEAR) and 69% (KEYNOTE 426), the subpopulations relevant for research question 2, patients with an intermediate or poor risk profile, make up the majority of the total population of both studies. However, these percentages are not large enough to allow rating the similarity of the 2 studies' subpopulations on the basis of the respective total populations. For the subpopulations, no data are available on patient characteristics, treatment

and follow-up observation durations, or on prior and subsequent therapies received. Therefore, the subpopulations cannot be inferred with acceptable certainty to be sufficiently similar for an indirect comparison.

Irrespective of this problem, it was impossible to draw any conclusions on added benefit regarding research question 1 or research question 2 from the indirect comparison of the CLEAR and KEYNOTE 426 studies for the outcomes of the morbidity, health-related quality of life, or side effects categories. For the KEYNOTE 426 study, no usable data on the outcomes of the morbidity and health-related quality of life categories are available in the study arms due to differing survey time points. For the outcomes of the side effects category, the high outcome-specific risk of bias results in insufficient certainty of results for the indirect comparison, at least on the side of the KEYNOTE 426 study [27]. Hence, even if the relevant subpopulations of the CLEAR and KEYNOTE 426 studies were assumed to be sufficiently similar, only the outcome of overall survival would be suitable for analysis. The results for the outcome of overall survival presented by the company's Module 4 A show no statistically significant difference between pembrolizumab + lenvatinib versus pembrolizumab + axitinib for the subpopulation relevant for research question 1 (favourable risk profile) nor for the subpopulation relevant for research question 2 (intermediate and poor risk profiles). In addition, an adequate weighing of benefit and harm would be impossible due to the lack of usability of results on the outcome categories of morbidity, health-related quality of life, and side effects.

2.4 Results on added benefit

No suitable data for the assessment of added benefit in comparison with the ACT are available for assessing pembrolizumab + lenvatinib in adults with previously untreated, advanced renal cell carcinoma with a favourable risk profile (research question 1) or in adults with an intermediate or poor risk profile (research question 2).

This results in no hint of added benefit of pembrolizumab + lenvatinib in comparison with the ACT for any of these patients; added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of added benefit of pembrolizumab + lenvatinib in comparison with the ACT is summarized in Table 9.

Table 9: Pembrolizumab + lenvatinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with previously untreated, advanced renal cell carcinoma with favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven
2	Adults with previously untreated, 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. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to 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. Against 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 assessment described above deviates from the company's assessment. While the latter likewise did not derive any added benefit from the analysis of the indirect comparison, in the overall picture of the indirect comparison as well as the direct comparison it additionally took into account, the company derived a non-quantifiable added benefit for each of the research questions.

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.

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