IQWiG Reports – Commission No. A21-160

Lenvatinib (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 *Lenvatinib (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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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 feedback was received in the framework of the present dossier assessment.

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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)

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 lenvatinib. 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 8 December 2021.

Research question

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

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

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

Research question	Therapeutic indication	ACT[a]
1	Adult patients with previously untreated advanced renal cell carcinoma and a favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib
2	Adult patients with previously untreated advanced renal cell carcinoma and an intermediate (IMDC score 1–2) or unfavourable risk profile (IMDC score ≥ 3)[b]	▪ Avelumab in combination with axitinib (only for patients with an unfavourable risk profile), or ▪ Nivolumab in combination with ipilimumab or ▪ **Pembrolizumab in combination with axitinib**

a. Presented is the respective ACT specified by the GBA. 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 these 2 risk groups (intermediate and unfavourable risk profile) differ with regard to their prognosis, making this a heterogeneous patient population. Against this background, the dossier was to present separate subgroup analyses for patients with intermediate risk profile and for those with unfavourable risk profile.

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

The company departs from the ACT specified by the G-BA. While the company concurred with the options specified by the G-BA by selecting pembrolizumab in combination with axitinib (hereinafter referred to as "pembrolizumab + axitinib") as the ACT for both research questions, it departed from the G-BA's specification by designating nivolumab + ipilimumab, pazopanib, pembrolizumab + axitinib as well as sunitinib as the ACT for lenvatinib + pembrolizumab in

the present therapeutic indication, irrespective of risk profile. In the company's view, sunitinib is an ACT of particular importance. This deviation is not appropriate. The company does not list any sources to adequately justify its deviation from the ACT specified by the G-BA. Regarding sunitinib, it must also be noted that each of the ACT options cited by the G-BA offered considerable added benefit in comparison with sunitinib. The German S3 guideline reflects these results by recommending sunitinib only for patients who are not candidates for checkpoint inhibitor-based combination therapy. However, the company's deviation remains without consequence because the company did not use the presented comparison with sunitinib for deriving any added benefit or greater or lesser harm. The present benefit assessment was carried out in comparison with the ACT specified by the G-BA for each of the separate research questions.

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 and study design

No relevant randomized controlled trial (RCT) was found for the direct comparison of lenvatinib + pembrolizumab 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 lenvatinib + pembrolizumab 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 in a 1:1:1 ratio to treatment with lenvatinib + everolimus (N = 357), lenvatinib + pembrolizumab (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 the lenvatinib + pembrolizumab arm or the sunitinib arm who have a favourable risk profile, defined as International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

score 0. A total of 110 patients in the lenvatinib + pembrolizumab arm and 124 patients in the sunitinib arm exhibited a favourable baseline risk profile according to the IMDC score.

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

KEYNOTE 426 study

The KEYNOTE 426 study is a randomized, open-label, active-control approval study comparing pembrolizumab + axitinib with sunitinib. The study included adults with advanced or metastatic clear-cell renal cell carcinoma (stage IV according to the American Joint Committee on Cancer [AJCC] classification system). Patients were not allowed to have received any prior systemic therapy at 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 with a KPS < 70% or with active brain metastases were excluded from the study.

A total of 861 patients were randomly allocated in 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 (IMDC 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 unfavourable 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 study is still ongoing. To date, 4 data cut-offs have been conducted. The company's Module 4 B, however, presents analyses predominantly for the 3rd data cut-off.

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.

The KEYNOTE 426 study is still ongoing. The company's Module 4 B presents analyses for the 2nd and 3rd data cut-off. For this purpose, the company used published data from benefit assessment procedures already completed for the present therapeutic indication, pembrolizumab from 2019 and cabozantinib from 2021, as well as the Powles 2020 publication.

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, no data on patient characteristics, treatment and follow-up durations, or prior and subsequent therapies received are available for the subpopulation relevant for research question 1 (favourable risk profile) nor for the subpopulation relevant for research question 2 (intermediate or unfavourable risk profile). 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 B show no statistically significant difference between lenvatinib + pembrolizumab 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 unfavourable risk profile).

Results

No suitable data for the assessment of added benefit in comparison with the ACT are available for assessing lenvatinib + pembrolizumab in adult patients with previously untreated advanced renal cell carcinoma with a favourable risk profile (research question 1) nor in adult patients with an intermediate or unfavourable risk profile (research question 2).

This results in no hint of added benefit of lenvatinib + pembrolizumab in comparison with the ACT for either of these groups; 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 added benefit of lenvatinib + pembrolizumab.

[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

Table 3: Lenvatinib + pembrolizumab – probability and extent of added benefit

Research question	**Therapeutic indication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult patients with previously untreated advanced renal cell carcinoma with a favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven
2	Adult patients with previously untreated advanced renal cell carcinoma and an intermediate (IMDC score 1–2) or unfavourable risk profile (IMDC score ≥ 3)[b]	▪ Avelumab in combination with axitinib (only for patients with unfavourable 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-A. 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 these 2 risk groups (intermediate and unfavourable risk profile) differ with regard to their prognosis, making this a heterogeneous patient population. Against this background, the dossier was to present separate subgroup analyses for patients with intermediate risk profile and for those with unfavourable risk profile.

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 added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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].

2.2 Research question

The aim of the present report is to assess the added benefit of lenvatinib in combination with pembrolizumab (hereinafter referred to as “lenvatinib + pembrolizumab”) in comparison with the appropriate comparator therapy (ACT) in adult patients 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 question of the benefit assessment of lenvatinib + pembrolizumab

Research question	Therapeutic indication	ACT[a]
1	Adult patients with previously untreated advanced renal cell carcinoma with a favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib
2	Adult patients with previously untreated advanced renal cell carcinoma and an intermediate (IMDC score 1–2) or unfavourable risk profile (IMDC score ≥ 3)[b]	▪ Avelumab in combination with axitinib (only for patients with an unfavourable 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 these 2 risk groups (intermediate and unfavourable risk profiles) differ with regard to their prognosis, making this a heterogeneous patient population. Against this background, the dossier was to present separate subgroup analyses for patients with intermediate risk profile and for those with unfavourable risk profile.

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

The company departs from the ACT specified by the G-BA. While the company concurred with the options specified by the G-BA by selecting pembrolizumab in combination with axitinib (hereinafter referred to as "pembrolizumab + axitinib") as the ACT for both research questions, it departed from the G-BA’s specification by designating nivolumab + ipilimumab, pazopanib, pembrolizumab + axitinib as well as sunitinib as the ACT for lenvatinib + pembrolizumab in the present therapeutic indication, irrespective of risk profile. In the company’s view, sunitinib is an ACT of particular importance. This deviation is not appropriate. The company does not list any sources to adequately justify its deviation from the ACT specified by the G-BA. Furthermore, it must be noted that the ACT options designated by the G-BA each showed considerable added benefit in comparison with 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]. However, the company’s deviation remains without consequence because the company did not use the presented comparison with sunitinib for deriving any added benefit or greater or lesser harm. The present benefit

assessment was carried out in comparison with the ACT specified by the G-BA for each of the separate research questions.

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 lenvatinib + pembrolizumab (status: 16 September 2021)
- bibliographical literature search on lenvatinib + pembrolizumab (last search on 16 September 2021)
- search in trial registries / trial results databases for studies on lenvatinib + pembrolizumab (last search on 16 September 2021)
- search on the G-BA website for lenvatinib + pembrolizumab (last search on 30 September 2021)
- bibliographical literature search on the ACT (last search on 16 September 2021)
- search in trial registries / trial results databases for studies on the ACT (last search on 16 September 2021)
- search on the G-BA website for the ACT (last search on 1 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 lenvatinib + pembrolizumab side and on the side of the ACT chosen by the company, pembrolizumab + axitinib. The check did not identify any additional relevant studies.

Direct comparison

The check of completeness of the study pool found no relevant randomized controlled trial (RCT) for the direct comparison of lenvatinib + pembrolizumab in comparison with the ACT specified by the G-BA. While the company likewise found no directly comparative RCTs including the ACT, the company's selection took into account only studies comparing with pembrolizumab + axitinib.

Yet, to illustrate medical benefit, the company presented the CLEAR study comparing lenvatinib + pembrolizumab versus sunitinib. In the present assessment of benefit versus the

ACT, the CLEAR study is relevant only for the indirect comparison, and therefore, it is discussed only in the context of the indirect comparison below.

Indirect comparison

Since the company did not find any RCTs comparing with pembrolizumab + axitinib, it looked for RCTs to be used in an adjusted indirect comparison. For this purpose, the company first looked for RCTs with the intervention to be assessed, lenvatinib + pembrolizumab, finding 1 relevant RCT in comparison with sunitinib:

- CLEAR (which the company referred to as study 307): lenvatinib + pembrolizumab versus sunitinib

For the indirect comparison, the company conducted an information retrieval for studies with pembrolizumab + axitinib and the common comparator of sunitinib. Restricting its search to the common comparator of sunitinib is appropriate because, in the check of completeness of the study pool, no further relevant RCT with lenvatinib + pembrolizumab and hence no further relevant common comparator was identified 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 relevant study on the comparison of pembrolizumab + axitinib versus sunitinib.

2.3.1 Studies included

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

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

Study	Study category			Available sources		
	Approval study for 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])
Lenvatinib + pembrolizumab vs. sunitinib						
E7080-G000-307 or KEYNOTE 581 (CLEAR[d])	Yes	Yes	No	Yes [7,8]	Yes [9-11]	Yes [12,13]
Pembrolizumab + axitinib vs. sunitinib						
MK-3475-426 (KEYNOTE 426[d])	No	No	Yes	No	Yes [14-17]	Yes [18-22]

a. Study sponsored by the company.
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. The company referred to the E7080-G000-307 study as study 307.

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 (A19-99) as well as in the context of an indirect comparison used in the benefit assessment of cabozantinib + nivolumab (A21-49) [23,24].

Figure 1 schematically presents the indirect comparison.

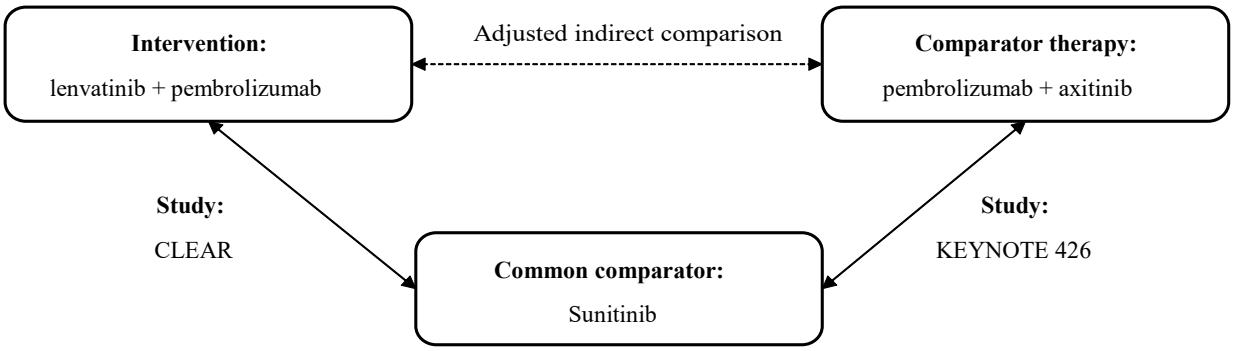

Figure 1: Study pool for the indirect comparison of lenvatinib + pembrolizumab versus pembrolizumab + axitinib

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: Study pool – RCT, indirect comparison: lenvatinib + pembrolizumab 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]
Lenvatinib + pembrolizumab vs. sunitinib						
CLEAR	RCT, open-label, parallel-group	Adults with previously untreated advanced renal cell carcinoma[b] and Karnofsky Performance Status ≥ 70%	Lenvatinib + pembrolizumab (N = 355) Lenvatinib + everolimus (N = 357)[c] Sunitinib (N = 357) Relevant subpopulations thereof: <u>Research question 1[d]:</u> Lenvatinib + pembrolizumab (n = 110) Sunitinib (n = 124) <u>Research question 2[e]:</u> Lenvatinib + pembrolizumab (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> 06/12/2018[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: Study pool – RCT, indirect comparison: lenvatinib + pembrolizumab 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]	Primary: overall survival, PFS Secondary: symptoms, health status, health-related quality of life, AEs

Table 6: Study pool – RCT, indirect comparison: lenvatinib + pembrolizumab 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 taking into account relevance for this benefit assessment. Secondary outcomes include information only 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 unfavourable 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. Prespecified 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. Prespecified 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. Prespecified 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. Prespecified 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. Prespecified interim analysis to be carried out after the occurrence of 74% of the events ultimately required in the outcome of overall survival (or 299 deaths). AE: adverse event; AJCC: American Joint Committee on Cancer; DOR: duration of response; EMA: European Medicines Agency; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; n: relevant subpopulation; N: number of randomized patients; ORR: objective response rate; PFS: progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: randomized controlled trial						

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

Study	Intervention / comparator therapy	Common comparator
Lenvatinib + pembrolizumab vs. sunitinib		
CLEAR	Lenvatinib 20 mg/day, orally + Pembrolizumab 200 mg every 3 weeks, i.v.	Sunitinib 50 mg/day, orally Duration of cycle: 6 weeks (4 weeks of treatment, followed by a 2-week break)
	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.	▪ 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 possible 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, pre-existing 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 lenvatinib + pembrolizumab arm: systemic corticosteroids (except for prophylactic therapy of allergic reactions and for the treatment of immune-mediated AEs) ▪ Other investigational preparations	

Table 7: Characteristics of the intervention – RCT, indirect comparison: lenvatinib + pembrolizumab 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	Sunitinib 50 mg/day, orally Duration of cycle: 6 weeks (4 weeks of treatment, followed by a 2-week break)
	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	▪ Treatment discontinuation or 2 dose reductions due to toxicity allowed in 12.5 mg increments down to the minimum dose of 25 mg, 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] ▪ Strong 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 (to pembrolizumab) in the intervention arm (antihistamines, analgesics) ▪ Symptomatic radiotherapy of individual lesions or of the brain after consultation with the sponsor **Nonpermitted concomitant treatment** ▪ Therapies that were not permitted as pretreatment ▪ Any systemic anticancer treatment ▪ Sunitinib arm only: antiarrhythmics ▪ Pembrolizumab + axitinib arm only: systemic glucocorticoids (except for prophylactic therapy of allergic reactions and for the treatment of AEs)	

Table 7: Characteristics of the intervention – RCT, indirect comparison: lenvatinib + pembrolizumab 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-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 lenvatinib + pembrolizumab 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 in a 1:1:1 ratio to treatment with lenvatinib + everolimus (N = 357), lenvatinib + pembrolizumab (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 unfavourable). The lenvatinib + everolimus treatment arm is irrelevant for the present benefit assessment and is not discussed hereinafter.

Lenvatinib + pembrolizumab treatment as well as sunitinib treatment was administered in accordance with the regimen presented in Table 7 and largely corresponds to SPC specifications [25-27].

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 lenvatinib + pembrolizumab arm) had reached 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

The company used the total population for deriving added benefit. It justified this approach by arguing that the characteristic of IMDC risk score is not a relevant effect modifier for the patient-relevant outcomes, citing the results of the CLEAR study it submitted on the direct comparison of lenvatinib + pembrolizumab versus sunitinib. The company did not submit any subgroup analyses on the basis of the indirect comparison. In the company's view, results on the total population can therefore be extrapolated to the subpopulations defined by the G-BA.

The company's reasoning on combining the patient populations of the 2 research questions is not sound. The lack of a relevant effect modification for the characteristic of IMDC risk score is not a sufficient reason for combining the populations. Irrespective of this issue, it must be noted that the company submitted 2 subgroup analyses on the IMDC risk score for the comparison of lenvatinib + pembrolizumab versus sunitinib. For the characteristic of IMDC risk score (favourable versus intermediate versus unfavourable), the analyses showed a statistically significant interaction for the outcome of overall survival, among others. In the characteristic of IMDC risk score grouping (favourable versus intermediate and unfavourable), no effect modification was found for the outcome of overall survival.

The relevant subpopulations for the benefit assessment are those defined by the G-BA in accordance with the two research questions.

For research question 1, the relevant subpopulation comprises patients in the CLEAR study's lenvatinib + pembrolizumab arm or sunitinib arm who have a favourable risk profile (IMDC score 0). The IMDC score was surveyed at baseline alongside the MSKCC score. A total of 110 patients in the lenvatinib + pembrolizumab 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 the lenvatinib + pembrolizumab arm or the sunitinib arm who have an intermediate (IMDC score 1 to 2) or unfavourable (IMDC score ≥ 3) risk profile. A total of 243 patients in the lenvatinib + pembrolizumab arm and 229 patients in the sunitinib arm exhibited an intermediate or unfavourable baseline risk profile according to the IMDC score.

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

KEYNOTE 426 study

The KEYNOTE 426 study is a randomized, open-label, active-control approval study comparing pembrolizumab + axitinib with 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 with a KPS < 70% or with active brain metastases were excluded from the study.

A total of 861 patients were randomly allocated in 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 baseline IMDC score (favourable versus intermediate versus unfavourable).

Pembrolizumab + axitinib treatment as well as sunitinib treatment was administered in accordance with the regimen shown in Table 7 and largely corresponds to SPC specifications [26-28].

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).

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 (IMDC 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 unfavourable risk profile (IMDC ≥ 3). These criteria were met by 294 patients in the pembrolizumab + axitinib arm and 298 patients in the sunitinib arm.

In Module 4 B, the company presents analyses on the 2 relevant subpopulations, but these are unsuitable for use in the benefit assessment in the present situation (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: lenvatinib + pembrolizumab vs. pembrolizumab + axitinib

Comparison **Study** **Outcome category** **Outcome**	**Planned follow-up observation**
Lenvatinib + pembrolizumab vs. sunitinib	
CLEAR	
Mortality	
Overall survival	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	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 90 days after the last dose of the study medication or until 30 days after the last dose of the study medication if a new antineoplastic therapy is started

AE: adverse event; EORTC: European 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 outcomes on morbidity, health-related quality of life, and side effects are systematically shortened in both studies since 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 or 120 days for SAEs in the CLEAR study). For these

outcomes, data are therefore available only for the shortened observation 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, a total of 4 data cut-offs have been carried out:

- 1st data cut-off (6 December 2018): prespecified 1st interim analysis of the first 88 patients in the lenvatinib + pembrolizumab arm with a median follow-up time of 12 months and a minimum duration of response of 6 months.
- 2nd data cut-off (15 November 2019): prespecified 2nd interim analysis to be performed 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): prespecified 3rd interim analysis and final analysis of 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.

For the CLEAR study, the company's Module 4 B presents analyses on the 3rd data cut-off. The company added the analyses of the 4th data cut-off merely for the outcome of overall survival, and only for the direct comparison of lenvatinib + pembrolizumab versus sunitinib, which it analysed additionally. For the indirect comparison of lenvatinib + pembrolizumab versus pembrolizumab + axitinib, the company used only the 3rd data cut-off.

This approach is not appropriate. According to the dossier template [29], 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.

KEYNOTE 426 study

The KEYNOTE 426 study is still ongoing. According to the company, 3 data cut-offs have been conducted t to date:

- 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): prespecified 2nd interim analysis after the occurrence of 487 PFS events and 74% of the final required events of the outcome of overall survival (or 299 deaths)

In Module 4 B, the company presents analyses of the 2nd data cut-off, using the published data on the 2019 pembrolizumab benefit assessment procedure in the present indication [19]. In addition, the company took into account information from the cabozantinib benefit assessment procedure in the present indication, with the KEYNOTE 426 study being analysed in an indirect comparison [24]. For the outcomes of overall survival, PFS, and objective response rate (ORR), the company presented additional analyses on the 3rd data cut-off, which it obtained from the Powles 2020 publication [21]. For the remaining outcomes, the company reports no data being available on the 3rd 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 [1,30]. 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 [31].

The CLEAR and KEYNOTE 426 studies share a similar 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 of sunitinib is similar as well. Detailed information on the study design and the interventions in the two studies can be found in Section 2.3.2.1.

The company used the comparison of the patient characteristics on the basis of the total population of both studies and assessed them as similar. Information on the patient characteristics are not available for the subpopulation relevant for research question 1 (favourable risk profile) nor for the subpopulation relevant for research question 2 (intermediate or unfavourable risk profile). The company did not discuss the extent to which the analysis of the total population reveals similarities between the patient populations with a favourable risk profile (research question 1) versus intermediate and unfavourable risk profiles (research question 2).

The company's approach is not appropriate. As already discussed in benefit assessment A21-49 [24], 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 unfavourable risk profile, make up the

majority of the total population of both studies. However, these percentages are not large enough to allow assessing the similarity of the subpopulations of the 2 studies on the basis of the respective total populations. For the subpopulations, no data are available on the patient characteristics, treatment and follow-up observation durations, or on prior and subsequent therapies received. Therefore, the subpopulations cannot be said 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 [23]. Hence, even if the relevant subpopulations of the CLEAR and KEYNOTE 426 studies were assumed to be sufficiently similar, an analysis would be possible only for the outcome of overall survival. The results for the outcome of overall survival presented by the company's Module 4 B show no statistically significant difference between lenvatinib + pembrolizumab 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 unfavourable 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 lenvatinib + pembrolizumab in adult patients with previously untreated advanced renal cell carcinoma with a favourable risk profile (research question 1) or in adult patients with an intermediate or unfavourable risk profile (research question 2).

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

2.5 Probability and extent of added benefit

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

Table 9: Lenvatinib + pembrolizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adult patients with previously untreated advanced renal cell carcinoma with a favourable risk profile (IMDC score 0)	Pembrolizumab in combination with axitinib	Added benefit not proven
2	Adult patients with previously untreated advanced renal cell carcinoma and an intermediate (IMDC score 1–2) or unfavourable risk profile (IMDC score ≥ 3)[b]	▪ Avelumab in combination with axitinib (only for patients with an unfavourable 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 these 2 risk groups (intermediate and unfavourable risk profiles) differ with regard to their prognosis, making this a heterogeneous patient population. Against this background, the dossier was to present separate subgroup analyses for patients with intermediate risk profile and for those with unfavourable risk profile.

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

The assessment described above deviates from that by the company, which derived a hint of considerable benefit for the total population, regardless of risk profile, based on the results on the PFS outcome.

The approach for the derivation of an overall conclusion on 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 6.1 [online]. 2022 [Accessed: 17.08.2022]. URL: https://www.iqwig.de/methoden/general-methods_version-6-1.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 – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Nivolumab (neues Anwendungsgebiet: Nierenzellkarzinom, in Kombination mit Ipilimumab, Erstlinienbehandlung) [online]. 2019 [Accessed: 18.01.2022]. URL: https://www.g-ba.de/downloads/39-261-3923/2019-08-15_AM-RL-XII_Nivolumab_D-439_BAnz.pdf.

4. 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: 18.01.2022]. URL: https://www.g-ba.de/downloads/39-261-4289/2020-05-14_AM-RL-XII_Pembrolizumab-RCC_D-502_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; Avelumab (neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinie, Kombination mit Axitinib) [online]. 2020 [Accessed: 18.01.2022]. URL: https://www.g-ba.de/downloads/39-261-4288/2020-05-14_AM-RL_XII_Avelumab_D-504_BAnz.pdf.

6. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF). S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms; Langversion 3.0 [online]. 2021 [Accessed: 17.03.2022]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Nierenzellkarzinom/Version_3/LL_Nierenzellkarzinom_Langversion_3.0.pdf.

7. Eisai. A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR); study E7080-G000-307/KEYNOTE 581; clinical study report [unpublished]. 2021.

8. Eisai. A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR); study E7080-G000-307/KEYNOTE 581; Zusatzanalysen [unpublished]. 2021.

9. Eisai. A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR) [online]. [Accessed: 08.02.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000916-14.

10. Eisai. Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma (CLEAR) [online]. 2021 [Accessed: 08.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02811861.

11. Eisai. A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects With Advanced Renal Cell Carcinoma [online]. 2021 [Accessed: 08.02.2022]. URL: https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-173807.

12. Motzer R, Alekseev B, Rha SY et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. N Engl J Med 2021; 384(14): 1289-1300. https://dx.doi.org/10.1056/NEJMoa2035716.

13. Grünwald V, Powles T, Choueiri TK et al. Lenvatinib plus everolimus or pembrolizumab versus sunitinib in advanced renal cell carcinoma: study design and rationale. Future Oncol 2019; 15(9): 929-941. https://dx.doi.org/10.2217/fon-2018-0745.

14. 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: 08.02.2022]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000588-17.

15. 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]. 2017 [Accessed: 08.02.2022]. URL: http://www.drks.de/DRKS00011432.

16. 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]. 2022 [Accessed: 08.02.2022]. URL: https://ClinicalTrials.gov/show/NCT02853331.

17. Merck Sharp & Dohme. A Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-426) [online]. [Accessed: 21.01.2022]. URL: https://www.pharmnet-bund.de/dynamic/de/arzneimittel-informationssystem/index.html.

18. Correction to Lancet Oncol 2020; 21: 1563-73. Lancet Oncol 2020; 21(12): e553. https://dx.doi.org/10.1016/S1470-2045(20)30699-9.

19. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Pembrolizumab (neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinie, Kombination mit Axitinib) [online]. 2020 [Accessed: 09.02.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/511/.

20. Gemeinsamer Bundesausschuss. Nutzenbewertungsverfahren zum Wirkstoff Cabozantinib (Neues Anwendungsgebiet: Nierenzellkarzinom, Erstlinienbehandlung, Kombination mit Nivolumab) [online]. 2021 [Accessed: 09.02.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/681/.

21. 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.

22. 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.

23. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pembrolizumab (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 17.03.2022]. URL: https://www.iqwig.de/download/a19-99_pembrolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

24. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Cabozantinib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 25.10.2021]. URL: https://www.iqwig.de/download/a21-49_cabozantinib_nutzenbewertung-35a-sgb-v_v1-1.pdf.

25. Eisai. Kisplyx 4 mg/10 mg Hartkapseln [online]. 2021 [Accessed: 06.01.2022]. URL: https://www.fachinfo.de/.

26. MSD. KEYTRUDA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung [online]. 2021 [Accessed: 19.01.2022]. URL: https://www.fachinfo.de/.

27. Pfizer. Sutent 12,5/25/37,5/50 mg Hartkapseln [online]. 2021 [Accessed: 08.02.2022]. URL: https://www.fachinfo.de/.

28. Pfizer. Inlyta 1/ 3/ 5/ 7 mg Filmtabletten [online]. 2021 [Accessed: 03.02.2022]. URL: https://www.fachinfo.de/.

29. Gemeinsamer Bundesausschuss. Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4; Dokumentvorlage, Version vom 21.02.2019 [online]. [Accessed: 02.03.2022]. URL: https://www.g-ba.de/downloads/17-98-4825/2019-02-21_Anl2_6_Modul4.pdf.

30. 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.

31. 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.

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