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Cabozantinib (renal cell carcinoma 1) –

Addendum to Commission A21-49[1]

Addendum

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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

IQWiG employees involved in the addendum

- Anne-Kathrin Petri
- Jona Lilienthal
- Regine Potthast
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
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)
PRO	patient-reported Outcome
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 8 September 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-49 (Upadacitinib– Benefit assessment according to §35a Social Code Book V) [1].

In the dossier assessment for the assessment of the added benefit of cabozantinib in combination with nivolumab in adult patients with treatment-naive advanced renal cell carcinoma, the adjusted indirect comparison based on the studies CheckMate 9ER [2] and KEYNOTE 426 [3,4] was used. The study CheckMate 9ER compares cabozantinib in combination with nivolumab (hereinafter referred to as "cabozantinib + nivolumab") vs. sunitinib. The study KEYNOTE-426 compares pembrolizumab in combination with axitinib (hereinafter referred to as "pembrolizumab + axitinib") vs. sunitinib.

In its comments [5], the pharmaceutical company (hereinafter referred to as "the company") submitted results of a third data cut-off on the CheckMate 9ER study in comparison with the dossier [6]. Moreover, another company that had submitted comments [7] described a fault in the dossier assessment regarding the documentation times in the patient-reported outcomes in the CheckMate 9ER study.

The G-BA therefore commissioned IQWiG to assess the following analyses presented by the company in the dossier [6] or in the commenting procedure [5]:

- Update of the results of the indirect comparison based on the third data cut-off of the CheckMate 9ER study (of 24 June 2021), if this data cut-off is suitable
- Assessment of the results of the indirect comparison (second data cut-off of the CheckMate 9ER study) on the PROs of the categories "morbidity" and "health-related quality of life" taking into account the data on the documentation times in the sunitinib arm of the CheckMate 9ER study

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Assessment of the results of the third data cut-off of the CheckMate 9ER study

With its comments [5], the company presented the results of a third data cut-off on the patient-relevant outcome "overall survival". The G-BA commissioned IQWiG to assess the data cut-off and, if suitable, to update the results of the indirect comparison.

Overall, the dossier assessment provided no suitable data for the assessment of the added benefit compared with the appropriate comparator therapy (ACT) for research question 1, as the similarity of the relevant subpopulations of the studies CheckMate 9ER and KEYNOTE 426 could not be assessed due to limited information on patient characteristics. Therefore, the data subsequently submitted at the third data cut-off have no consequence for this research question.

For research question 2, the second data cut-off of the studies CheckMate 9ER study was used for the assessment of the added benefit in the dossier assessment [1]. The third data cut-off presented on this outcome by the company took place on 24 June 2021 and thus about 9 months after the second data cut-off (10 September 2020) used in the dossier assessment. Information on treatment and observation periods are not available for the third data cut-off.

The concrete reason for the conduction of a third data cut-off at this time point is unclear. Neither the company's comments nor the oral hearing [8] provide any information on whether this data cut-off was the prespecified final data cut-off of the CheckMate 9ER study. According to the study protocol [2], this final data cut-off was to take place after 254 deaths for the outcome "overall survival". At the third data cut-off presented, a total of 271 deaths had occurred in the CheckMate 9ER study.

For research question 2, the results of the indirect comparison for the outcome "overall survival" under consideration of the third data cut-off of the CheckMate 9ER study are presented in Appendix A of the full dossier assessment.

Assessment of the results of the indirect comparison on PROs

In the CheckMate 9ER study, the PROs "health status" (recorded using the visual analogue scale [VAS] of the EQ-5D) and "symptoms" (recorded using the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms [FKSI-DRS]) were recorded.

The data presented by the company for the CheckMate 9ER study are overall usable.

In the cabozantinib + nivolumab arm of the CheckMate 9ER study, cabozantinib was administered continuously and nivolumab was administered every 2 weeks. The PROs were recorded every 2 weeks, i.e. each time before nivolumab was administered.

In the comparator arm, sunitinib was continuously administered for 4 weeks of a 6-week cycle, followed by a 2 weeks off therapy. In the sunitinib arm, the PROs were recorded every 6 weeks, i.e. each time before the 4-week treatment phase.

The data on the PROs in the CheckMate 9ER study were thus collected at different times in each of the study arms. However, for the dossier, the company only analysed the results on the common documentation times of both arms (i.e. every 6 weeks).

The analysed documentation time (every 6 weeks) for the patients in both study arms took place before the administration or at intervals of 2 weeks after administration of a potentially troublesome therapy, respectively. Therefore, it can be assumed that the burden of the treatment during the course of the cycle was represented comparably in both study arms at the time of recording.

KEYNOTE-426, in contrast, provides no usable data on the PROs. This is due to unequal documentation times in the respective study arms, which result in unequal burdens of the patients (detailed description see A19-99 [9]).

Consequently, there are no data for the indirect comparison, since only the data of the intervention study CheckMate 9ER are available. Moreover, both the CheckMate 9ER study and the KEYNOTE-426 study are unblinded studies. This would result in a high risk of bias for the results of the PROs in both studies. This means that, in addition, the requirements for the certainty of results for carrying out an indirect comparison would not be met.

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of cabozantinib from dossier assessment A21-49.

The following Table 1 shows the result of the benefit assessment of cabozantinib under consideration of dossier assessment A21-49 and the present addendum.

Table 1: Cabozantinib + nivolumab – probability and extent of added benefit

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

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. The G-BA pointed out that the two risk groups (intermediate and poor risk profile) differ with regard to their prognosis, which results in a heterogeneous patient population. Before this background, subgroup analyses for patients with intermediate and poor risk profiles were to be presented in the dossier.
c. The studies CheckMate 9ER and KEYNOTE-426 only included patients with RCC with clear-cell component and a Karnofsky performance status ≥ 70%. It remains unclear whether the observed effects can be transferred to patients without clear-cell component and a Karnofsky performance status < 70 %.

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

The G-BA decides on the added benefit.

3 References

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-119.html.

Appendix A: Results on the outcome "overall survival" for research question 2

Results

Table 2 summarizes the results for the comparison of cabozantinib + nivolumab with pembrolizumab + axitinib in patients with treatment-naive advanced renal cell carcinoma with intermediate or poor risk profile.

Table 2: Results on overall survival – RCT, indirect comparison: cabozantinib + nivolumab vs. pembrolizumab + axitinib

Outcome category **Outcome** **Comparison** **Study**	**Cabozantinib + nivolumab or pembrolizumab + axitinib**		**Sunitinib**		**Group difference**
	N	**Median time to event in months [95 % CI][a]** **patients with event n (%)**	**N**	**Median time to event in months [95 % CI][a]** **pPatients with event n (%)**	**HR [95% CI][b]; p-value[c]**
Mortality					
Overall survival					
Cabozantinib + nivolumab vs. sunitinib					
CheckMate 9ER (data cut-off 24 June 2021)	249[d]	37.55 [32.53; NC] 100 (40.2)	256[d]	29.04 [23.39; 36.17] 131 (51.2)	0.66 [0.50; 0.85]; 0.002
Pembrolizumab + axitinib vs. sunitinib					
KEYNOTE-426 (data cut-off 6 January 2020)	294[d]	ND 116 (39.5)	298[d]	ND 154 (51.7)	0.63 [0.50; 0.81]; < 0.001
Indirect comparison using common comparators[e]:					
Cabozantinib + nivolumab vs. pembrolizumab + axitinib					1.05 [0.73; 1.50]

a. Median and 95% CI: unstratified product limit estimate in the CheckMate 9ER study.
b. HR and 95% CI: Cox proportional hazards model in the CheckMate 9ER study stratified by IMDC prognostic risk score (1–2, 3–6), PD-L1 tumour expression (≥ 1%, < 1% or undetermined) and region (USA/Canada/Western Europe/Northern Europe, rest of the world) according to IRT.
c. In the CheckMate 9ER study calculated using the log-rank test, stratified by IMDC prognosis risk score (1-2, 3-6), PD-L1 tumour expression (≥ 1%, < 1% or undetermined) and region (USA/Canada/Western Europe/Northern Europe, rest of the world) according to IRT; in the KEYNOTE 426 study calculated using the Wald test.
d. Number of randomized patients in the subpopulation according to research question 2.
e. Indirect comparison according to Bucher [10].

CI: confidence interval; HR: hazard ratio; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IRT: Interactive Response Technology; N: number of patients who received at least one dose of the study medication; n: number of patients with (at least 1) event; NC: not calculable; ND: no data; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial

Subgroups and other effect modifiers

Research question 2 comprised patients with intermediate and poor risk profile according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score. These risk

groups differ with regard to their prognosis. The G-BA pointed out that subgroup analyses for patients with intermediate and poor risk profiles were to be presented for the dossier assessment (see also Table 1).

In the comments, the company presented no calculations of the interaction values for the adjusted indirect comparison. However, for research question 2, it presented results separately for the subpopulation of patients with intermediate (IMDC score 1-2) and poor risk profile (IMDC score ≥ 3). This resulted in no statistically significant difference between cabozantinib + nivolumab and pembrolizumab + axitinib. The Institute's calculation revealed no statistically significant interaction.