IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Tivozanib (renal cell carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Tivozanib (Nierenzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 January 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	mechanistic target of rapamycin
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VEGFR	vascular endothelial growth factor receptor

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tivozanib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 2 November 2017.

Research question

The aim of the present report was to assess the added benefit of tivozanib in comparison with the appropriate comparator therapy (ACT) as first-line treatment of adult patients with advanced renal cell carcinoma and for adult patients who are vascular endothelial growth factor receptor (VEGFR) and mechanistic target of rapamycin (mTOR) pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma.

For the benefit assessment of tivozanib, the research questions presented in Table 2 resulted from the ACTs specified by the G-BA.

Table 2: Research questions of the benefit assessment of tivozanib

Research question	**Subindication**	**ACT[a]**
1	First-line treatment of patients with favourable or intermediate prognosis (MSKCC score 0–2)	Bevacizumab in combination with interferon alfa-2a *or* monotherapy with pazopanib *or* **sunitinib**
2	First-line treatment of patients with unfavourable prognosis (MSKCC score ≥ 3)	Temsirolimus
3	In disease progression in VEGFR and mTOR pathway inhibitor-naive patients after one prior treatment with cytokine therapy	Axitinib *or* **sorafenib**

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**.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MSKCC: Memorial Sloan Kettering Cancer Center; mTOR: mechanistic target of rapamycin; VEGFR: vascular endothelial growth factor receptor

The company followed the G-BA's specification of the ACT. From the G-BA's options, the company chose sunitinib as ACT for research question 1, and sorafenib as ACT for research question 3.

However, the company defined research question 3 as "patients with advanced renal cell carcinoma after pretreatment with cytokines". According to the Summary of Product Characteristics (SPC), the therapeutic indication of research question 3 includes patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after one prior

treatment with cytokine therapy for advanced renal cell carcinoma. The therapeutic indication specified in the approval was the basis for the research question of the benefit assessment.

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

Results for research question 1: first-line treatment of patients with favourable or intermediate prognosis (MSKCC score 0–2)

Study pool of the company

No directly comparative data were available for the assessment of the added benefit of tivozanib in comparison with the ACT in patients with advanced renal cell carcinoma in first-line treatment with favourable or intermediate prognosis (Memorial Sloan Kettering Cancer Center [MSKCC] score 0–2).

The company therefore presented an adjusted indirect comparison of tivozanib versus sunitinib using sorafenib as common comparator. On the side of the intervention, the company included the randomized controlled trial (RCT) TIVO-1, which compared tivozanib with sorafenib and, with a subpopulation, concurred with the present research question. On the side of the comparator therapy, the company included the RCT SWITCH. The SWITCH study compared 2 treatment sequences: sunitinib followed by sorafenib versus sorafenib followed by sunitinib. The company used the data on the first-line treatment (sunitinib versus sorafenib) for the indirect comparison.

The indirect comparison presented by the company was unsuitable to draw conclusions on the added benefit of tivozanib in comparison with the ACT. Hereinafter, the studies included by the company are described in more detail, presenting the reasons for not including the indirect comparison for the benefit assessment.

Description of the studies included by the company

Study TIVO-1 on tivozanib

The TIVO-1 study was an open-label RCT on the comparison of tivozanib (N = 260) versus sorafenib (N = 257). It included adult patients with recurrent or metastatic renal cell carcinoma who had not received prior treatment with VEGFR or mTOR pathway inhibitors and who had received no more than one prior systemic treatment for metastatic renal cell carcinoma. The company used a subpopulation of the TIVO-1 study for the adjusted indirect comparison (N = 181 patients from each study arm).

Study SWITCH on sunitinib

The SWITCH study was a randomized, controlled sequential study. The study compared sunitinib followed by sorafenib (N = 183) with sorafenib followed by sunitinib (N = 182). It included adult patients with advanced or metastatic renal cell carcinoma without prior systemic treatment who were unsuitable for cytokine therapy. According to the information provided in

the publication, 97% of the patients had a favourable or intermediate prognosis based on their MSKCC score, which is in compliance with the research question. The second-line treatment (sorafenib or sunitinib) specified in the intervention was administered after progression or unacceptable toxicity under the first-line treatment (sunitinib or sorafenib). The company only used the data on the first-line treatment for the indirect comparison.

Reasons for the lack of suitability of the indirect comparison presented by the company

There were no usable data on the outcome categories of mortality, morbidity and health-related quality of life

Regarding patient-relevant outcomes, the company only presented the results on side effects available in both studies for the adjusted indirect comparison of tivozanib with sunitinib.

No usable data on overall survival were available in the SWITCH study for the adjusted indirect comparison presented by the company because the publication presented data on overall survival only for the treatment sequences (sunitinib-sorafenib and sorafenib-sunitinib), but not for the first-line treatment.

Outcomes on symptoms or health-related quality of life were not reported in the publication on the SWITCH study.

Hence for the adjusted indirect comparison presented by the company, relevant data were only available for the outcome category of side effects. No conclusions could be drawn on the outcome categories of mortality, morbidity and health-related quality of life. An overall balancing and a conclusion on the added benefit of tivozanib in comparison with the ACT was therefore not possible and the adjusted indirect comparison was unusable.

Further aspects

- At least for the TIVO-1 study, the risk of bias of the adverse event (AE) outcomes used by the company (serious adverse events [SAEs] and severe AEs) was rated as high. The indirect comparison presented by the company consisted of only one study for each direct comparison (tivozanib versus sorafenib, and ACT versus sorafenib). Since only results with high risk of bias were available for one of the studies included and hence for one of the direct comparisons, the indirect comparison presented did not meet the minimum requirement of the certainty of results for the derivation of a hint.
- Sufficient similarity of the analysed study populations in TIVO-1 and SWITCH is doubtful:
  - The mean treatment period with sorafenib (common comparator) differed notably between both studies.
  - For the outcome “SAEs”, the 2 studies showed a notable imbalance in the proportions of patients with event in the respective common comparator arms.
  - It was unclear which definition of the MSKCC score was used in the SWITCH study and for the data on the TIVO-1 study presented by the company in Module 4 A.

Results for research question 2: First-line treatment of patients with unfavourable prognosis (MSKCC score ≥ 3)

No data were available for the assessment of the added benefit of tivozanib in comparison with the ACT in patients with advanced renal cell carcinoma in first-line treatment with unfavourable prognosis (MSKCC score ≥ 3). This resulted in no hint of an added benefit of tivozanib in comparison with the ACT; an added benefit is therefore not proven.

Results for research question 3: VEGFR and mTOR pathway inhibitor-naive patients with disease progression after one prior treatment with cytokine therapy

Study pool of the company

The company presented the RCT TIVO-1 for research question 3. The RCT was unsuitable to draw conclusions on the added benefit of tivozanib in comparison with the ACT in adult VEGFR and mTOR pathway inhibitor-naive patients with disease progression following one prior treatment with cytokine therapy for the advanced renal cell carcinoma.

Hereinafter, the study included by the company is described in more detail, presenting the reasons for not using the study for the benefit assessment.

Study TIVO-1

The TIVO-1 study was an open-label RCT on the comparison of tivozanib (N = 260) versus sorafenib (N = 257). It included adult patients with recurrent or metastatic renal cell carcinoma who had not received prior treatment with VEGFR or mTOR pathway inhibitors and who had received no more than one prior systemic treatment for metastatic renal cell carcinoma. For research question 3, the company presented analyses of a subpopulation of the TIVO-1 study (tivozanib arm: N = 79, sorafenib arm: N =75).

No transferability of the results of the TIVO-1 study to research question 3 of the benefit assessment

According to the SPC of tivozanib, the population relevant for research question 3 comprises patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma. The criterion of disease progression after cytokine therapy was no inclusion criterion of the TIVO-1 study. Information on disease progression after cytokine therapy was also not recorded in the study. In addition, it was unclear whether all patients had received cytokine therapy for advanced renal cell carcinoma. Hence based on the information provided in the study documents, the subpopulation relevant for research question 3 cannot be identified in the RCT presented. This issue was not addressed in the company's dossier. In Module 4 A, the company defined the population of "patients after cytokine pretreatment" from the TIVO-1 study ,without considering the restrictions of prior disease progression and the fact that cytokine therapy was to be administered for advanced renal cell carcinoma. The company also did not discuss whether the analysed population concurred with the population of the therapeutic indication.

Since the results of the subpopulation of the TIVO-1 study presented in Module 4 A were not transferable to the population relevant for research question 3, the results were not used for the present benefit assessment. A more detailed investigation of the transferability is not relevant, however, as cytokine therapy is hardly used anymore in the current German health care context.

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

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

Table 3 presents a summary of the probability and extent of the added benefit of tivozanib.

Table 3: Tivozanib – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
First-line treatment of patients with favourable or intermediate prognosis (MSKCC score 0–2)	Bevacizumab in combination with interferon alfa-2a *or* monotherapy with pazopanib *or* **sunitinib**	Added benefit not proven
First-line treatment of patients with unfavourable prognosis (MSKCC score ≥ 3)	Temsirolimus	Added benefit not proven
In disease progression in VEGFR and mTOR pathway inhibitor-naive patients after one prior treatment with cytokine therapy	Axitinib *or* **sorafenib**	Added benefit not proven
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MSKCC: Memorial Sloan Kettering Cancer Center; mTOR: mechanistic target of rapamycin; VEGFR: vascular endothelial growth factor receptor		

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of the present report was to assess the added benefit of tivozanib in comparison with the ACT as first-line treatment of adult patients with advanced renal cell carcinoma for adult patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma.

For the benefit assessment of tivozanib, the research questions presented in Table 4 resulted from the ACTs specified by the G-BA.

Table 4: Research questions of the benefit assessment of tivozanib

Research question	**Subindication**	**ACT[a]**
1	First-line treatment of patients with favourable or intermediate prognosis (MSKCC score 0–2)	Bevacizumab in combination with interferon alfa-2a *or* monotherapy with pazopanib *or* **sunitinib**
2	First-line treatment of patients with unfavourable prognosis (MSKCC score ≥ 3)	Temsirolimus
3	In disease progression in VEGFR and mTOR pathway inhibitor-naive patients after one prior treatment with cytokine therapy	Axitinib *or* **sorafenib**
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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MSKCC: Memorial Sloan Kettering Cancer Center; mTOR: mechanistic target of rapamycin; VEGFR: vascular endothelial growth factor receptor		

The company followed the G-BA's specification of the ACT. From the G-BA's options, the company chose sunitinib as ACT for research question 1, and sorafenib as ACT for research question 3.

However, the company defined research question 3 as "patients with advanced renal cell carcinoma after pretreatment with cytokines". According to the SPC [3], the therapeutic indication of research question 3 includes patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma (see Section 2.7.2.1 of the full dossier assessment). The therapeutic indication specified in the approval was the basis for the research question of the benefit assessment.

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

2.3 Research question 1: first-line treatment of patients with favourable or intermediate prognosis (MSKCC score 0–2)

2.3.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on tivozanib (status: 21 August 2017)
- bibliographical literature search on tivozanib (last search on 15 August 2017)
- search in trial registries for studies on tivozanib (last search on 21 August 2017)
- bibliographical literature search on ACTs (last search on 15 August 2017)
- search in trial registries for studies on ACTs (last search on 21 August 2017)

To check the completeness of the study pool:

- search in trial registries for studies on tivozanib (last search on 10 November 2017)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of tivozanib versus the ACT for the first-line treatment of patients with advanced renal cell carcinoma and favourable or intermediate prognosis (MSKCC score 0–2).

The adjusted indirect comparison presented by the company was unsuitable to derive an added benefit of tivozanib in comparison with the ACT. This is justified below.

Study pool of the company

In its information retrieval, the company identified no studies of direct comparison of tivozanib versus the ACT for research question 1. For this reason, the company conducted an information retrieval for a possible adjusted indirect comparison.

On the side of the intervention, the company identified the RCT TIVO-1 [4,5], which compared tivozanib with sorafenib and, with a subpopulation, concurred with the present research question. Since the TIVO-1 study was the only relevant RCT on tivozanib including patients concurring with the present research question, sorafenib was the only possible common comparator for an indirect comparison.

On the side of the comparator therapy, the company identified 2 RCTs (SWITCH [6,7] and ASSURE [8-10]) that might be considered for a possible adjusted indirect comparison using the common comparator sorafenib. The ASSURE study compared sunitinib with sorafenib. Since the publications available for the ASSURE study contained no information on the prognosis status according to the MSKCC score, and no classification of the patient population

according to research question 1 was therefore possible, the company did not use the ASSURE study for an indirect comparison. This approach is comprehensible.

The SWITCH study compared 2 treatment sequences: sunitinib followed by sorafenib versus sorafenib followed by sunitinib. The company used the data on the first-line treatment (sunitinib versus sorafenib) for the indirect comparison.

Using a subpopulation of the TIVO-1 study and part of the observation period of the SWITCH study, the company therefore presented an adjusted indirect comparison with the common comparator sorafenib for the assessment of the added benefit of tivozanib versus sorafenib.

Hereinafter, the studies included by the company are described in more detail, presenting the reasons for not including the indirect comparison for the benefit assessment.

Description of the studies included by the company

Study TIVO-1 on tivozanib

The TIVO-1 study was an open-label RCT on the comparison of tivozanib (N = 260) versus sorafenib (N = 257). It included adult patients with recurrent or metastatic renal cell carcinoma who had not received prior treatment with VEGFR or mTOR pathway inhibitors and who had received no more than one prior systemic treatment for metastatic renal cell carcinoma. A description of the characteristics of the study can be found in Appendix A (Table 9 and Table 10) of the full dossier assessment.

The company used a subpopulation of the TIVO-1 study for the adjusted indirect comparison (N = 181 patients from each study arm). The company provided no further information on the formation of the subpopulation. However, the patient characteristics presented in Module 4 A showed that it consisted of treatment-naive patients with an MSKCC score of 0–2.

Study SWITCH on sunitinib

The SWITCH study was a randomized, controlled sequential study. The study compared sunitinib followed by sorafenib (N = 183) with sorafenib followed by sunitinib (N = 182). It included adult patients with advanced or metastatic renal cell carcinoma without prior systemic treatment who were unsuitable for cytokine therapy. According to the information provided in the publication [7], 97% of the patients had a favourable or intermediate prognosis based on their MSKCC score, which is in compliance with the research question. The second-line treatment (sorafenib or sunitinib) specified in the intervention was administered after progression or unacceptable toxicity under the first-line treatment (sunitinib or sorafenib) (see Figure 1).

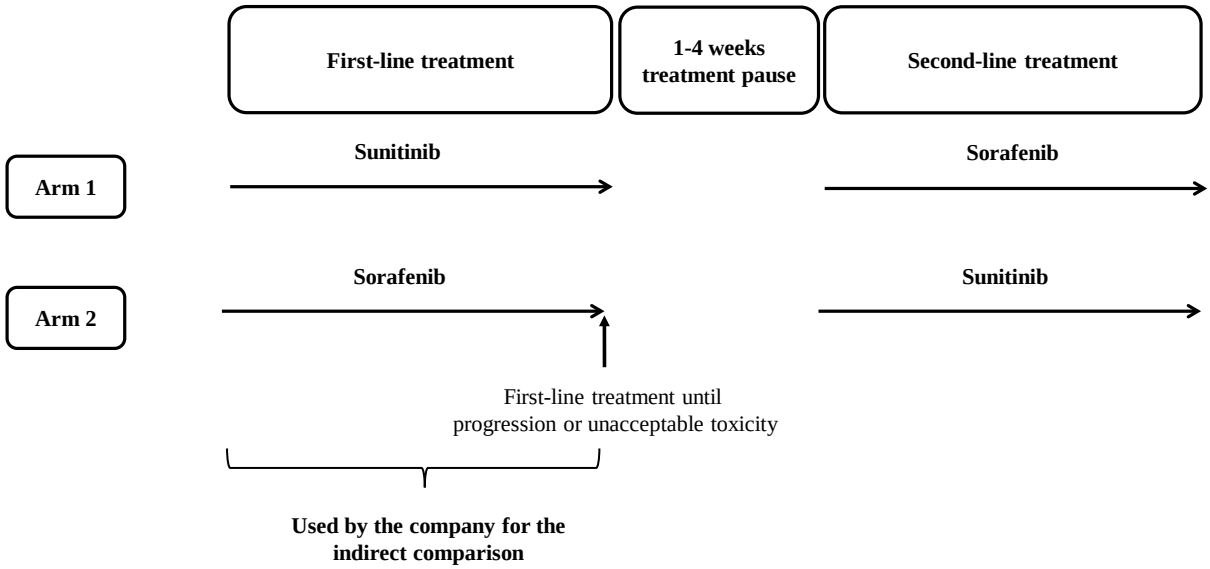

Figure 1: Study design of the SWITCH study and data used by the company

The company only used the data on the first-line treatment for the indirect comparison because the comparison of treatment sequences (sunitinib-sorafenib versus sorafenib-sunitinib) was not relevant for the present indirect comparison. This approach is principally comprehensible; the consequences resulting from this, however, are described below.

Reasons for the lack of suitability of the indirect comparison presented by the company

There were no usable data on the outcome categories of mortality, morbidity and health-related quality of life

The company presented results for progression-free survival (PFS) and for outcomes on side effects available in both studies for the adjusted indirect comparison of tivozanib with sunitinib.

No usable data on overall survival were available in the SWITCH study [6,7] for the adjusted indirect comparison presented by the company because the publication [7] presented data on overall survival only for the treatment sequences (sunitinib-sorafenib and sorafenib-sunitinib), but not for the first-line treatment. The company's assessment that the results on overall survival for the treatment sequences were not relevant for the present research question is adequate. Even the results on overall survival for the first-line treatment alone would not allow an adequate comparison with the TIVO-1 study as there was no follow-up observation.

Furthermore, the company did not present the results on overall survival for the subpopulation of the TIVO-1 study analysed by the company. According to the company, no usable data were available due to the allowed treatment switching in the study (according to the company, over 60% of the patients in the subpopulation switched from sorafenib to tivozanib after the end of treatment). This assessment of the company is not comprehensible particularly because it considered the results of the TIVO-1 study on overall survival as usable for research question 3, although 61% of the patients switched treatment from sorafenib to tivozanib also in the subpopulation for this research question.

Outcomes on symptoms or health-related quality of life were not defined as outcomes of the SWITCH study in the publication.

The data on PFS presented by the company were not usable as, in both studies included by the company, PFS was determined only based on imaging techniques and not based on symptoms noticeable by the patients. The outcome in the present operationalization was therefore not considered as patient-relevant outcome.

Hence for the adjusted indirect comparison presented by the company, relevant data were only available for the outcome category of side effects. No conclusions could be drawn on the outcome categories of mortality, morbidity and health-related quality of life. An overall balancing and a conclusion on the added benefit of tivozanib in comparison with the ACT was therefore not possible and the adjusted indirect comparison was unusable.

Further aspects

At least for the TIVO-1 study, the risk of bias of the AE outcomes used by the company (SAEs and severe AEs) was rated as high because the median treatment durations in the total population differed notably between the treatment arms (52 weeks in the tivozanib arm versus 41 weeks in the sorafenib arm). The open-label study design caused potential bias for the outcome "discontinuation due to AEs". The indirect comparison presented by the company consisted of only one study for each direct comparison (tivozanib versus sorafenib, and ACT versus sorafenib). Since only results with high risk of bias were available for one of the studies included and hence for one of the direct comparisons, the indirect comparison presented did not meet the minimum requirement of the certainty of results for the derivation of a hint.

Besides, sufficient similarity of the analysed study populations in TIVO-1 and SWITCH is doubtful:

- The mean treatment period with sorafenib (common comparator) differed notably between both studies: Whereas the mean treatment duration with sorafenib was 37.5 weeks for patients in the SWITCH study, it was 54.8 weeks for patients in the TIVO-1 study (information for the total population; the respective information for the subpopulation was not available). In both studies, the treatment duration depended on the time point of progression or unacceptable toxicity.
- For the outcome "SAEs", the 2 studies showed a notable imbalance in the respective common comparator arms: 21% of the patients in the subpopulation of the TIVO-1 study analysed by the company for research question 1 had an SAE under treatment with sorafenib versus 50% of the patients in the SWITCH study.
- It was unclear which definition of the MSKCC score was used in the SWITCH study and for the data on the TIVO-1 study presented by the company in Module 4 A. The clinical study report (CSR) on the TIVO-1 study cites different definitions of the MSKCC score. The company did not address this issue.

2.3.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of tivozanib in comparison with the ACT in patients with advanced renal cell carcinoma in first-line treatment with favourable or intermediate prognosis (MSKCC score 0–2). This resulted in no hint of an added benefit of tivozanib in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of tivozanib in comparison with the ACT in patients with advanced renal cell carcinoma in first-line treatment with favourable or intermediate prognosis (MSKCC score 0–2), an added benefit of tivozanib is not proven for these patients.

This assessment deviates from that of the company, which derived a hint of considerable added benefit on the basis of the indirect comparison presented.

2.3.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.4 Research question 2: first-line treatment of patients with unfavourable prognosis (MSKCC score ≥ 3)

2.4.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on tivozanib (status: 21 August 2017)
- bibliographical literature search on tivozanib (last search on 15 August 2017)
- search in trial registries for studies on tivozanib (last search on 21 August 2017)
- bibliographical literature search on the ACT (last search on 15 August 2017)
- search in trial registries for studies on the ACT (last search on 21 August 2017)

To check the completeness of the study pool:

- search in trial registries for studies on tivozanib (last search on 10 November 2017)

In its information retrieval, the company identified no studies of direct comparison of tivozanib versus the ACT for research question 2. The Institute's check of completeness also identified no RCTs of direct comparison of tivozanib versus the ACT for this research question.

For a possible adjusted indirect comparison, the company identified the TIVO-1 study on the comparison of tivozanib versus sorafenib. However, the company identified no studies on temsirolimus, the ACT specified for research question 2, that was suitable for an adjusted indirect comparison using the common comparator sorafenib and hence presented no indirect comparison. In addition, the company described in a different section that only one patient from the TIVO-1 study was available for this research question. Hence, due to missing data on tivozanib, no meaningful indirect comparison would have been possible anyway. The company also presented no further investigations.

2.4.2 Results on added benefit

The company presented no data for the assessment of the added benefit of tivozanib in comparison with the ACT in patients with advanced renal cell carcinoma in first-line treatment with unfavourable prognosis (MSKCC score ≥ 3). This resulted in no hint of an added benefit of tivozanib in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of tivozanib in comparison with the ACT in patients with advanced renal cell carcinoma in first-line treatment with unfavourable prognosis (MSKCC score ≥ 3), an added benefit of tivozanib is not proven for these patients.

This assessment corresponds to that of the company.

2.4.4 List of included studies

Not applicable as the company presented no data for the benefit assessment.

2.5 Research question 3: VEGFR and mTOR pathway inhibitor-naive patients with disease progression after one prior treatment with cytokine therapy

2.5.1 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on tivozanib (status: 21 August 2017)
- bibliographical literature search on tivozanib (last search on 15 August 2017)
- search in trial registries for studies on tivozanib (last search on 21 August 2017)

To check the completeness of the study pool:

- search in trial registries for studies on tivozanib (last search on 10 November 2017)

No relevant study was identified from the check.

Study pool of the company

From the steps of information retrieval mentioned, the company identified the RCT TIVO-1 [4,5].

The RCT presented by the company was unsuitable to draw conclusions on the added benefit of tivozanib in comparison with the ACT in adult VEGFR and mTOR pathway inhibitor-naive patients with disease progression following one prior treatment with cytokine therapy for the advanced renal cell carcinoma.

Hereinafter, the study included by the company is described in more detail, presenting the reasons for not using the study for the benefit assessment.

Study TIVO-1

The TIVO-1 study was an open-label RCT on the comparison of tivozanib (N = 260) versus sorafenib (N = 257). It included adult patients with recurrent or metastatic renal cell carcinoma who had not received prior treatment with VEGFR or mTOR pathway inhibitors and who had received no more than one prior systemic treatment for metastatic renal cell carcinoma.

Treatment in both study arms was largely conducted in accordance with the respective SPCs [3,11]. Treatment with tivozanib or sorafenib was to be conducted until death, unacceptable toxicity, confirmed disease progression, treatment failure at the physician's discretion, discontinuation at the patient's request, or end of study. The maximum treatment duration planned was 2 years. Patients who received their randomized treatment for 2 years and showed clinical benefit and acceptable tolerance could continue treatment within the framework of an extension study (study AV-951-09-902 [12]). In the framework of the extension study, patients in the sorafenib arm could be switched to tivozanib after progression. The company described in Module 4 A that, in the subpopulation analysed for the present research question (see next section for a description of this subpopulation), 34% of the patients in the tivozanib arm and 64% of the patients in the sorafenib arm had subsequent therapy. 61% of the patients in the sorafenib arm switched treatment to tivozanib.

The characteristics of the study and of the interventions of the TIVO-1 study are presented in Appendix A (Tables 9 and 10) of the full dossier assessment.

Subpopulation of the TIVO-1 study analysed by the company

For research question 3, the company presented analyses of a subpopulation of the TIVO-1 study (tivozanib arm: N = 79, sorafenib arm: N =75). It designated the population as "patients after cytokine pretreatment" without providing further information on the formation of this subpopulation, however. It can be assumed that the company included all patients with at least one prior therapy in the subpopulation (one patient in the tivozanib arm had 2 prior therapies). According to the inclusion criteria of the TIVO-1 study, prior therapy was not restricted to cytokines. It can be inferred from the study documents and the European Public Assessment

Report (EPAR) [13] that the proportion of patients who had a different prior therapy than cytokines was negligible, however.

No transferability of the results of the TIVO-1 study to research question 3 of the benefit assessment

According to the SPC of tivozanib [3], the population relevant for research question 3 comprises patients who are VEGFR and mTOR pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma.

Concurring with this, only patients who were VEGF and mTOR pathway inhibitor-naive were included in the TIVO-1 study.

However, the criterion of disease progression after cytokine therapy was no inclusion criterion of the study. Information on disease progression after cytokine therapy was also not recorded in the study. It is therefore possible that patients without disease progression after cytokine therapy were included in the study.

Besides, it was unclear whether all patients had received cytokine therapy for advanced renal cell carcinoma. According to the inclusion criteria of the TIVO-1 study, patients with postoperative or adjuvant treatment were also rated as pretreated for the metastatic disease if recurrence occurred within 6 months after completion of treatment. It could be inferred from the study documents that a relevant proportion of patients received their prior therapy in the adjuvant setting.

Hence based on the information provided in the study documents, the subpopulation relevant for research question 3 cannot be identified in the RCT presented.

This issue was not addressed in the company's dossier. In Module 4 A, the company defined the population of "patients after cytokine pretreatment" from the TIVO-1 study, without considering the restrictions of prior disease progression after cytokine therapy for advanced renal cell carcinoma and without discussing whether the analysed population concurred with the population of the therapeutic indication.

Since the results of the subpopulation of the TIVO-1 study presented in Module 4 A were not transferable to the population relevant for research question 3, the results were not used for the present benefit assessment. A more detailed investigation of the transferability is not relevant, however, as cytokine therapy is hardly used anymore in the current German health care context. The company also considered this research question as having no future relevance.

The results of the subpopulation of the TIVO-1 study analysed by the company („patients after cytokine pretreatment") are presented in Appendix A of the full dossier assessment.

Notes on the results presented by the company

In the TIVO-1 study, analyses were conducted at several time points:

- data cut-off in December 2011: planned as analysis of the primary outcome "PFS" (planned after 310 events) and interim analysis for overall survival
- data cut-off in August 2012: planned as final analysis for overall survival (2 years after inclusion of the last patient)
- data cut-off in July 2013 (post-hoc analysis)

In Module 4 A, the company described that the analyses presented for the subpopulation analysed by the company (population C, "patients after cytokine pretreatment") were at the data cut-off in January 2015 for all outcomes. However, the CSR cites July 2013 as the latest data cut-off date for patient-reported outcomes and overall survival. Recording of patient-reported outcomes beyond this time point was also not planned. A comparison of the data on the total population between Module 4 A and the CSR also showed that the results on overall survival in Module 4 A were based on the data cut-off in July 2013; according to information provided in the CSR, only AE analyses were based on data recorded until January 2015. Neither the data cut-off in July 2013 nor the time point of subsequent AE recording until January 2015 was prespecified.

2.5.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of tivozanib in comparison with the ACT in adult VEGFR and mTOR pathway inhibitor-naive patients with disease progression following one prior treatment with cytokine therapy for the advanced renal cell carcinoma. This resulted in no hint of an added benefit of tivozanib in comparison with the ACT; an added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of tivozanib in comparison with the ACT in adult VEGFR and mTOR pathway inhibitor-naive patients with disease progression following one prior treatment with cytokine therapy for the advanced renal cell carcinoma, an added benefit of tivozanib is not proven for these patients.

This assessment deviates from that of the company, which derived an indication of a major added benefit for the subpopulation of the TIVO-1 study analysed ("patients after cytokine pretreatment").

2.5.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of tivozanib in comparison with the ACT in patients with advanced renal cell carcinoma is summarized in Table 5.

Table 5: Tivozanib – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
First-line treatment of patients with favourable or intermediate prognosis (MSKCC score 0–2)	Bevacizumab in combination with interferon alfa-2a *or* monotherapy with pazopanib *or* **sunitinib**	Added benefit not proven
First-line treatment of patients with unfavourable prognosis (MSKCC score ≥ 3)	Temsirolimus	Added benefit not proven
In disease progression in VEGFR and mTOR pathway inhibitor-naive patients after one prior treatment with cytokine therapy	Axitinib *or* **sorafenib**	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the pharmaceutical company (hereinafter referred to as "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**. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; MSKCC: Memorial Sloan Kettering Cancer Center; mTOR: mechanistic target of rapamycin; VEGFR: vascular endothelial growth factor receptor		

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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